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Short-term exposure to ozone in relation to mortality and out-of-hospital cardiac arrest

Exploring sensitive subgroups by previous hospitalizations

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SHORT-TERM EXPOSURE TO OZONE IN RELATION TO MORTALITY AND OUT-OF-HOSPITAL CARDIAC ARREST: EXPLORING SENSITIVE SUBGROUPS BY PREVIOUS HOSPITALIZATIONS

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I dedicate this thesis to my parents, who made it possible with their relentless and dedicated efforts throughout my life; to my husband, Shahid Raza, for motivating me to pursue doctoral education and for his guidance and persistent support; and to my sons, Azan and Muhammad, my ultimate source of pride and joy.

Strive always to excel in virtue and truth
The Last Prophet (peace be upon him)

ABSTRACT

Background: Several epidemiological studies have associated short-term ozone (O_3) exposure with mortality, as well as with out-of-hospital cardiac arrest (OHCA) and other morbidity. Knowledge on which parts of the general population that are susceptible to adverse O_3-related health effects is scarce.

Aim: The aim of this thesis is to explore the role of previous disease in conferring susceptibility to O_3 exposure in relation to total, cardiovascular and respiratory mortality, and OHCA.

Materials and Methods: We obtained information on age, sex, date and cause of death [classified using the International Classification of Diseases, Ninth (ICD-9) and Tenth Revision (ICD-10)] on all non-traumatic deaths that occurred in Stockholm County from 1990 to 2010. We considered all non-traumatic deaths, as well as cardiovascular and respiratory deaths separately. Data on all Emergency Medical Service-assessed OHCA were obtained from the Swedish Register for Cardiopulmonary Resuscitation. We included all OHCAs that occurred in Stockholm County from 2000 to 2014, and all OHCA occurring in 2006-2014 in Gothenburg and Malmö. All deaths and OHCA were linked to their previous hospitalizations as recorded in the National Patient Register, using personal identification numbers. Hourly values of O_3 were obtained from single urban background monitoring stations in each city. We generated daily 8-h maximum levels as well as 2-h, 24-h, 2d, and 7d means. The associations between ambient O_3 levels and health outcomes were estimated with time-series analyses using generalized additive and linear models, and with time-stratified case-crossover analysis.

Results: Short-term increases in O_3 levels were associated with increased risks of total, cardiovascular and respiratory mortality, irrespective of previous hospitalizations. Individuals previously hospitalized for myocardial infarction demonstrated a higher O_3-related risk of total and cardiovascular mortality in comparison with the general population (1.7 % vs 0.5 %; 2.1 % vs 0.8 %, per 10 $\mu g/m^3$ increase in O_3 during a 2d period). Individuals with previous hospitalization for chronic obstructive pulmonary disease exhibited higher risk of O_3-related respiratory mortality compared to the general population (5.5 % vs 2.7 %). Furthermore, O_3 exposure was associated with OHCA. A 10 $\mu g/m^3$ increase of 2-h and 24-h averaged O_3 was associated with an odds-ratio of 1.02 (95% CI: 1.01, 1.05) and 1.04 (95% CI: 1.01 – 1.07), respectively. We did not however observe a difference in O_3-related risk of OHCA in individuals hospitalized for any of the pre-specified diagnoses of acute myocardial infarction, heart failure, diabetes, hypertension, or stroke, in comparison with the general population.

Conclusions: Our results suggest that previous hospitalizations for myocardial infarction or chronic obstructive pulmonary disease increases the susceptibility for mortality following short-term exposure to O_3. In contrast, previous hospitalizations for cardiovascular diseases did not seem to modify the associations between short-term increases in O_3 levels and the risk out-of-hospital cardiac arrest.

LIST OF SCIENTIFIC PAPERS

I. Bero Bedada G, **Raza A**, Forsberg B, Lind T, Ljungman P, Pershagen G, Bellander T. Short-term exposure to ozone and mortality in subjects with and without previous cardiovascular disease. *Epidemiology. 2016;27(5):663-9*

II. **Raza A**, Dahlquist M, Lind T, Ljungman P. Susceptibility to short-term ozone exposure and cardiovascular and respiratory mortality by previous hospitalizations. *Submitted*

III. **Raza A**, Bellander T, Bero-Bedada G, Dahlquist M, Hollenberg J, Jonsson M, Lind T, Rosenqvist M, Svensson L, Ljungman P. Short-term effects of air pollution on out-of-hospital cardiac arrest in Stockholm. *Eur Heart J. 2014;35(13):861-8.*

IV. **Raza A**, Dahlquist M, Jonsson M, Hollenberg J, Svensson L, Lind T, Ljungman P. Ozone and cardiac arrest: The role of previous hospitalizations. *Submitted*

CONTENTS

LIST OF ABBREVIATIONS

APHEA	The Air Pollution and Health a European Approach
APHENA	The Air Pollution and Health a European and North American Approach
AMI	Acute Myocardial Infarction
AQG	Air Quality Guidelines
CH_4	Methane
CI	Confidence Interval
CO	Carbon monoxide
COPD	Chronic Obstructive Pulmonary Disease
CPR	Cardiopulmonary Resuscitation
CVD	Cardiovascular Disease
EMS	Emergency Medical Service
ICD	Implantable Cardioverter Defibrillators
ICD-9	International Classification of Disease, Ninth Revision
ICD-10	International Classification of Disease, Tenth Revision
NMHC	Non-methane Hydrocarbons
NPR	The National Patient Register
NO	Nitrogen Oxide
NO_2	Nitrogen Dioxide
OR	Odds Ratios
OHCA	Out-of-Hospital Cardiac Arrest
O_3	Ozone
PANs	Peroxy-acetyl Nitrates
PM_{10}	Particulate Matter with an aerodynamic diameter ≤ 10 μm
$PM_{2.5}$	Particulate Matter with an aerodynamic diameter ≤ 2.5 μm
$PM_{0.1}$	Particulate Matter with an aerodynamic diameter ≤ 0.1 μm
SO_2	Sulphur Dioxide
SRCR	Swedish Register for Cardiopulmonary Resuscitation
VOC	Volatile Organic Compounds
WHO	World Health Organization

1 INTRODUCTION

Air pollution is a major environmental threat to human health, and now ranks amongst the top global health risk burdens. A systematic analysis of major global health risks concluded that fine particulate matter pollution account for >3 million premature deaths globally and over 74 million years of healthy life lost. The main causes of air pollution-related mortality are cerebrovascular disease that accounted for 1.31 million deaths and ischemic heart disease that lead to 1.08 million deaths. This underlines that the vast majority of air pollution deaths are due to cardiovascular diseases [1]. The American Heart Association scientific statements in 2004 and 2010 provided several lines of evidence on the causal relationship between exposure to particulate matter and cardiovascular morbidity and mortality [2]. Cardiovascular disease is also a leading cause of mortality in Europe and North America. It is responsible for over 4 million deaths per year in Europe which is almost half the total mortality rate [3]. In Sweden, about 3,500 premature deaths per year are related to particulate matter air pollution. [4]. Ozone (O_3) exposure has also recently received attention as an emerging threat.

1.1 AIR POLLUTION IN GENERAL

Air pollution is defined as a complex mixture of gases, liquids and solid particles suspended in air at levels that pose risk to human health. These chemical compounds are called air pollutants and are broadly classified into particles and gases. Particles are classified according to the size of their aerodynamic diameter expressed as particulate matter equal to or less than 10 micrometers in diameter (PM_{10}), fine particles ($PM_{2.5}$), coarse particles ($PM_{10} - PM_{2.5}$), and ultrafine particles ($PM_{0.1}$). Gases generally include nitric oxide (NO), nitrogen dioxide (NO_2), carbon monoxide (CO), sulphur dioxide (SO_2), and O_3. Household combustion, traffic, industrial processes and forest fires are common sources of these air pollutants. Pollutants of major public health concern are particulate matter, CO, O_3, NO_2, and SO_2. In our study setting we have very lows levels of air pollution except for O_3 and it is the only pollutant we observed associations with. Therefore, the focus of this thesis is on susceptibility to the adverse effects of O_3.

1.2 OZONE

Ozone is a highly reactive oxidant gas which in the stratosphere (10-16 kilometres above Earth's surface) acts as a protective shield against the harmful ultraviolet radiations emitted by the sun. However, O_3 close to Earth's surface is an air pollutant and is associated with multitude of health effects [5].

1.2.1 Ozone Formation

Ground-level O_3 is a secondary air pollutant formed at ground level by complex chemical reactions involving precursor compounds, such as nitrogen oxides and hydrocarbons, in the presence of sunlight. Formation of O_3 requires a free oxygen atom (O) that may be provided by the dissociation of nitrogen dioxide (NO_2) in the presence of sunlight.

$$NO_2 + h\nu\ (\lambda < 420\ nm) \rightarrow O + NO$$

The free oxygen atom and nitrogen oxide (NO) then react with molecular oxygen (O_2) and produce O_3. M is a non-reactive molecule that takes up the energy released in the reaction.

$$O + O_2 + M \rightarrow O_3 + M$$

In the presence of NO O_3 reacts with NO and forms NO_2

$$O_3 + NO \rightarrow O_2 + NO_2$$

In a closed system, these reactions thus merely recycle O_3 and NO_x and do not result in net production of O_3. Net O_3 production occurs in the presence of other precursors such as carbon monoxide (CO), methane (CH_4), non-methane hydrocarbons (NMHC), or certain other volatile organic compounds (VOC). Ambient O_3 concentrations formed by these chemical compounds are directly influenced by temperature, solar radiation, wind speed, and other meteorological factors. A simplified schematic pattern of O_3 formation is presented in Figure 1.1.

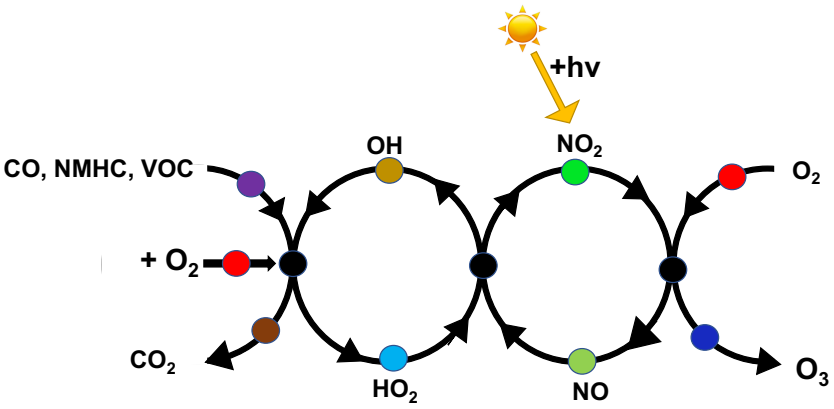

Figure 1.1 Ozone Formation

Close to combustion sources, the background O_3 is reduced by directly emitted NO to form NO_2, while away from the source and in the presence of sufficient VOCs and under favorable weather conditions NO_x emissions lead to rise in O_3 concentrations [6].

1.2.2 Precursors and Ozone Transport

Nitrogen oxides can be transported to remote areas as a reservoir species, such as peroxy-acetyl nitrates (PANs). These are a significant source of NO_x, and together with naturally released biogenic VOCs, form O_3 in non-polluted areas [6]. Ozone can also be transported to areas far away from where it originally formed and even across continents [7]. Some of the O_3 measured in Europe has its origins in North America and Asia [7, 8]. At times stratospheric O_3 descends down to ground level, resulting in comparatively high concentrations also in the absence of O_3 formation at ground level, particularly in remote unpolluted areas [9].

1.2.3 Spatial and Temporal Variability

Background O_3 levels have large spatial and temporal variability. Variations in O_3 concentrations are driven by the changes in the balance of its chemical productions and loss processes as air mass moves to and from different locations [9]. This balance is highly sensitive to the level of sunlight in a region [9]. Levels are generally high in the vicinity of urban environments where precursor emissions are high. Ozone levels increase with increased VOCs levels and intense sunlight but NO_x emissions affect both formation and destruction of O_3. In trafficated environments O_3 levels are low due to NO emissions which consume O_3. In rural areas close to precursor emissions O_3 concentration is higher due to lack of O_3 predators such as NO. Some areas are also influenced by the transport of air masses containing precursor emissions and additional biogenic VOCs emissions that further increase O_3 levels.

Ozone exhibits typical diurnal variability with higher levels during afternoon when photochemical activity is intense. The formation during the day is also driven by higher precursor emissions. Ozone has clear seasonal patterns with higher levels during the summer months when there is more sunlight.

1.2.4 Relationship Between Ozone Precursors and Ozone Concentrations

Since 1980s anthropogenic O_3 precursor emissions have reduced significantly in European countries but have not resulted in equivalent reductions in O_3 levels [6]. This is attributed to increased intercontinental transport of O_3 and its precursors [10] showing that trends in European O_3 levels cannot be entirely explained by changes in European precursor emissions. Increase in the levels of background O_3 along the Atlantic borders of Europe is influenced by the increased NO_x emissions in North America and Asia [11]. Furthermore, reductions in European NO_x emissions lead to low NO concentrations resulting in increased O_3 levels in urban environments in southern, central, and north-western parts of Europe [12, 13]. Other factors likely to mask the effects of European measures to reduce anthropogenic O_3 precursor emissions are climate variability, non-methane VOCs emissions from vegetation , and fire plumes from biomass and forest fires [14].

In Sweden, the situation is equally complicated. High O_3 levels have been observed at Esrange, in the northern part of Sweden. This area is far from pollution source areas and indicates the influence of long-range transport of O_3 [15, 16] and the contribution of stratospheric O_3 [17]. Ozone coming to Stockholm is mostly transported by the air originating from southeast of Europe, particularly during the summer months (Figure 1.2) [18]. There is some local formation of O_3 during spring and summer but is relatively small and slow due to less days with high temperatures and is least likely to affect Sweden's summer O_3 levels. Polluted air masses containing NO_x emissions from European and regional sources and with additional local sources of NO_x emissions act as a temporary sink for O_3 during winter in stable weather conditions [15].

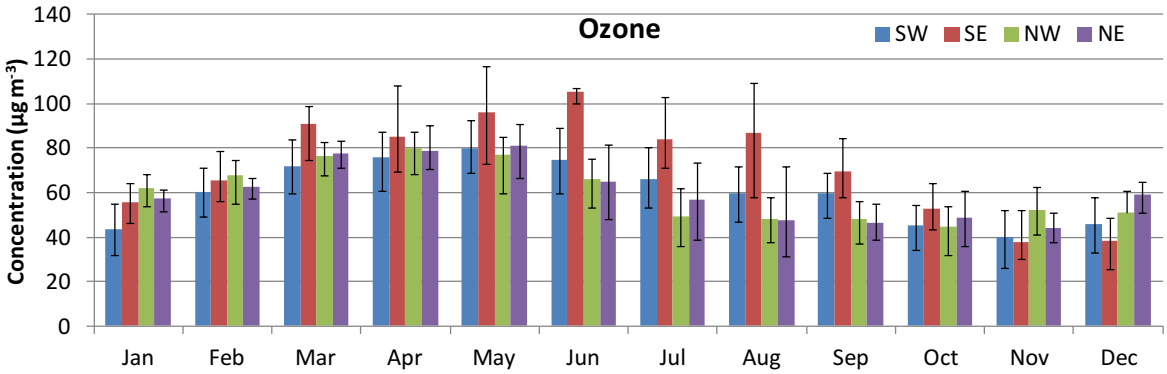

Figure 1.2 Monthly median concentrations of 8-h maximum O_3 concentrations in the four trajectory sectors with origin at Aspvreten (SW: Southwest; SE: Southeast; NW: Northwest; NE: Northeast) averaged over all available data in the period 1997-2010. Vertical bars are 75 and 25 percentiles. Source: Jönsson O, et al Boreal environment research. 2013;18(3-4):280-302.

1.2.5 Air Quality Guidelines

The World Health Organization (WHO) published its first air quality guidelines (AQG) in 1987 based on scientific evidence. Most high-income countries have considerably reduced their air pollution levels since then [19, 20]. Total emissions of O_3 precursor gases (NO_x, SO_2, and non-methane VOCs) in Europe reduced by 29% between 1990 and 2000 [19] and a decline in particulate matter and its precursors has also been observed [19]. However, since 2000 the air quality in Sweden and elsewhere in Europe has improved more discretely [21]. Presently, the air pollution levels in many traffic environments are still high, both in Sweden and elsewhere in Europe [21]. Large percentages of the EU urban population are exposed to levels exceeding the current WHO AQG value [22] of 100 µg/m^3 (as a daily 8-h maximum) for O_3 (O_3, 95%) [20] (Table 1.1). Ozone levels, however, remained below the WHO AQG in Sweden during the last decade. Despite this, current levels of O_3 have been associated with adverse health outcomes even at levels below the AQG in Sweden and other countries [23, 24] and there is no evidence at this stage to support a threshold below which no health effects are expected [25]. Indeed it has been suggested that the exposure response relationship strengthens at lower levels [25].

Table 1.1 Ambient air quality standard for daily 8-h maximum average of O_3 levels in µg/m^3 by WHO (Air Quality Guideline 2005), EU-directive, and the US environmental protection agency.

Pollutant	WHO	European	US
Ozone	100	120	140

1.2.6 Population Exposure

Studies of short-term health effects of ambient air pollution commonly employ two different exposure assessment strategies. For smaller panel studies, exposure may be assessed through personal monitoring. This requires that participants are able to carry portable monitoring equipment for a specified time period. While this may provide more precise personal exposure it has several drawbacks: It necessitates a selection of participants able and willing to wear the equipment, it measures outdoor and as well as indoors sources with some difficulty of separation, it limits the time-frame and sample size of exposure assessment and is costly and logistically challenging. Large studies of rare events such as mortality or hospital admissions are not amenable to this strategy and instead make use of time-series of continuous exposure measurements from strategically located fixed monitoring stations. Typically, studies use monitors situated at roof-tops or similar, capturing the average urban background level. In an urban environment, the temporal variability of O_3 over a period of hours to a few weeks is generally large in comparison with the variability in the spatial gradient, even over a large urban fabric. Owing to the comparatively smooth spatial distribution of O_3, these monitors therefore capture the relative temporal changes in ambient O_3 levels for a large geographical area. Apart from temporal and spatial variability of ambient O_3, indoor O_3 levels are substantially lower than outdoor levels. However, the overwhelming majority of the subsequently discussed studies have employed centrally located roof-level monitors reflecting urban background levels to assess O_3 exposure.

1.3 HEALTH EFFECTS OF OZONE EXPOSURE

1.3.1 Mortality

Positive associations between short-term exposure to O_3 and all-cause mortality were consistently observed in recent multicity time-series studies, conducted in several European [26, 27], in 80 US cities [28], and a multi-continental study [29]. These studies reported higher risk estimates for mortality stratified by warm or summer seasons. In relation to cause-specific mortality, O_3 exposure has been associated in many studies with respiratory mortality including the Air Pollution and Health: a European and North American Approach (APHENA) study [30] and other large multicity studies from the U.S [31], Europe [32], Italy [33], and Asia [34]. Furthermore, studies demonstrated positive associations for cardiovascular mortality in single pollutant, all year, and summer season analyses, also in multipollutant models including PM_{10} [30-33]. However, in the APHENA study cardiovascular mortality risk estimates in U.S. and Canadian datasets were sensitive to the inclusion of PM_{10} in the model [30].

1.3.2 Morbidity

1.3.2.1 Cardiac arrest

Cardiac arrest is a leading cause of cardiovascular death and in Sweden about 10,000 cardiac arrests occur annually with a 3-16% survival to one month [35]. Studies investigating the

association between transient air pollution exposure and the risk of out-of-hospital cardiac arrest (OHCA) have been conducted in the United States [36-40], Europe [41-43], Australia [44, 45], and Asia [46]. Studies from New York city [39], Indianapolis [38], and Houston [36] observed elevated risk of OHCA with increased levels of $PM_{2.5}$ on the hour of or 1-3 days before the cardiac arrest. The Houston study also found strong associations with O_3 at very short time intervals within hours [36]. All the US studies used daily averages as their exposure metric except the Houston study that used hourly means. A study from Helsinki, Finland reported O_3 exposure associated with increased risk of OHCA of cardiac origin other than AMI in 1 and 2 day lag, no association was reported for hourly lags [41]. A study conducted in Copenhagen, Denmark did not observe O_3 exposure with OHCA, however, reported fractions of particulate matter associated with OHCA at lag 3 and 4 day [42]. Large studies from Melbourne [44] and Perth [45], Australia observed strong associations with $PM_{2.5}$, however, no effect was observed with O_3. The study from Melbourne used daily averages for exposure windows and the study from Perth used hourly means. Furthermore, a study from Okayama, Japan reported associations with O_3 for 72-96 hours lags and 48 to 72 hours for $PM_{2.5}$ [47]. In Beijing, China with high air pollution levels a study used daily averages and observed strong associations between $PM_{2.5}$ at lag day-1 and cardiac arrest, while no associations were observed with O_3. [48]. A study from Seoul, South Korea, did not observe association with O_3 in any lags, however, reported association between $PM_{2.5}$ exposure and OHCA [49].

1.3.2.2 Other morbidities

Other observed adverse health effects of O_3 include changes in pro-arrhythmic measures, for instance decreased heart rate variability [50], association with ventricular arrhythmias in patients with implantable cardioverter defibrillators [51, 52], reduced lung capacity in children and adults [53, 54], increased risk of COPD-related emergency and hospital admissions [55, 56], increased risk of myocardial infarction [57], and increased emergency department visits for cardiovascular and respiratory diseases [58].

1.4 SUSCEPTIBLE POPULATIONS

There may be susceptible groups in general populations which are at higher risk of mortality or OHCA and might carry a major burden of negative effects of O_3 exposure.

1.4.1 Based on Individual Characteristics

Individual characteristics may plausibly increase susceptibility to mortality following O_3 exposure. Studies investigating sex differences related to O_3, NO_2, SO_2, and particulate matter (PM) exposure provided inconsistent findings [33, 59, 60]. Some studies observed higher susceptibility in women [33, 61] while other reported no sex differences [62, 63].

Aging processes are generally expected to contribute to an increased vulnerability of elderly people for environmental changes [64]. Elderly [23, 33, 65, 66] have thus been consistently reported as a high-risk group for the adverse effects of air pollution. Studies of other

pollutants than O_3 have reported increased risk of death in individuals ≥ 65 years of age as compared to younger age group on exposure to PM, NO_2, and SO_2 [59] and increased risk of out-of-hospital coronary deaths in both 65-74- and 75+-yr age groups exposed to PM [67]. A recent meta-analysis of O_3 and mortality reported higher risks in older as compared to the younger population [68]. Studies from Italy [33, 69] and US [70] also reported higher O_3-related mortality among elderly.

1.4.2 Based on Existing Diseases

Previous diseases might play an important role in individuals' susceptibility towards O_3-related risks of mortality or OHCA. Several studies have investigated O_3 exposure and total and cardiorespiratory mortality [27, 29, 71, 72], OHCA [73-76], and other morbidities [5, 77-81], but studies focusing on risks based on individuals' previous diseases are rare. In one study secondary causes of death were used as surrogates for previous diseases [70] and in two other studies previous disease histories were used [33, 69]. Pre-existing diseases that conferred increased susceptibility in these studies were not fully consistent from study to study but centered around diabetes, atrial fibrillation and atherosclerotic diseases [33, 69, 70]. Furthermore, no study investigated the effect modification of previous disease on the risk of OHCA following O_3 exposure, however, previous disease history for diabetes, hypertension, and stroke [48, 49] have been reported to confer susceptibility to $PM_{2.5}$-related risk of OHCA.

1.5 GAPS

Several studies have consistently associated O_3 exposure with total and cardiovascular mortality while results on respiratory mortality have been inconsistent and a majority of studies were limited to the warm season. At the time we planned our study projects, there were few studies [44, 82-85] that examined associations between air pollution and OHCA and none of them investigated the effects of O_3 exposure on OHCA. Existing OHCA studies used small data sets and daily averages for exposure, which carries a risk of exposure misclassification. There was a lack of knowledge on effects of exposure with short-temporal resolution on OHCA. Furthermore, higher susceptibility to harmful effects of air pollution among groups of individuals with pre-existing disease was rarely addressed. Existing studies have not considered cause-specific mortality, have been conducted in high pollution environments and have used secondary diagnoses or have not had access to full coverage patient and death registries. Knowledge on susceptible populations is important to provide relevant guidelines for air quality standards protecting significant susceptible groups within the general population in a low pollution setting.

2 AIMS

The overall aim was to investigate acute risks of mortality and cardiac arrest associated with O_3 exposure, and whether such risks are modified by previous disease manifestations.

Specific aims were:

- To estimate associations between short-term exposure to ambient O_3, and total, cardiovascular, and respiratory mortality
- To assess the role of previous hospitalizations in conferring susceptibility to O_3-related total, cardiovascular, and respiratory mortality
- To examine the association between short-term exposure to ambient O_3 and out-of-hospital cardiac arrest
- To assess the role of previous hospitalizations in conferring susceptibility to O_3-related risk of out-of-hospital cardiac arrest

3 MATERIAL AND METHODS

The first part of this sections summarizes outcome and exposure data with brief descriptions of their source and study populations along with time period of each study. Subsequently describe the statistical methods and analyses. Detailed descriptions are in the accompanying articles and manuscripts.

3.1 OUTCOME AND EXPOSURE DATA

3.1.1 Mortality

Studies I and II considered mortality outcomes in Stockholm County. We included all residents of Stockholm County who are older than 30 years of age and died in the County between 1990 and 2010. We obtained information on age, sex, date and cause of death [classified using the International Classification of Diseases, Ninth (ICD-9) and Tenth Revision (ICD-10)] from the Cause of Death Register [86]. For study I, we considered all non-traumatic deaths (ICD-9 codes 1–799; ICD-10 codes: A00-R99), while for study II, we considered cardiovascular (ICD-9 390-459, ICD-10 I00-I99) and respiratory (ICD-9 460-519, ICD-10 J00-J99) deaths separately.

3.1.2 Out-of-Hospital Cardiac Arrests

Studies III and IV considered out-of-hospital cardiac arrest as disease outcomes. All Emergency Medical Service (EMS)-assessed OHCA were obtained from the Swedish Register for Cardiopulmonary Resuscitation (SRCR). Cases are continuously registered in the SRCR if cardiopulmonary resuscitation (CPR) and/or defibrillation is attempted. The register also contained cardiac arrests where CPR was performed by a witness but not by the paramedics due to clear sign of death. From the register, we obtained information on gender, age, time and location of OHCA, status of patient when EMS-personnel arrived, and probable cause as evaluated by the EMS staff. Study III included all OHCA occurring in Stockholm County from 2000 to 2010. Study IV included all OHCA that occurred in Stockholm, Gothenburg and Malmö from 2006 to 2014.

Inclusion criteria in both OHCA studies was based on etiology and the time of cardiac arrest (Figure 3.1). We only included cases that had been assessed as cardiac. In our dataset, we had 33 time variables from three sources i) EMS-personnel, ii) police and iii) fire brigade. It was important to use a time closest to the actual time of OHCA as we used 2-hr exposure before the cardiac arrest and we did not want to include the exposure after the cardiac arrest in our case period. EMS-personnel are trained to record the time at each step of their response starting from the call to the arrival at the hospital, therefore, we used the time provided by the EMS-personnel. Moreover, to further avoid exposure temporal misclassification, we excluded cases that were dead (rigor mortis) when the EMS-personnel arrived. Cases with missing time data were also excluded. We used the time of cardiac arrest as the time dispatch center received the call or the communication between the ambulance and the emergency dispatch.

When this information was not available we used the time when ambulance arrived at the location of the event.

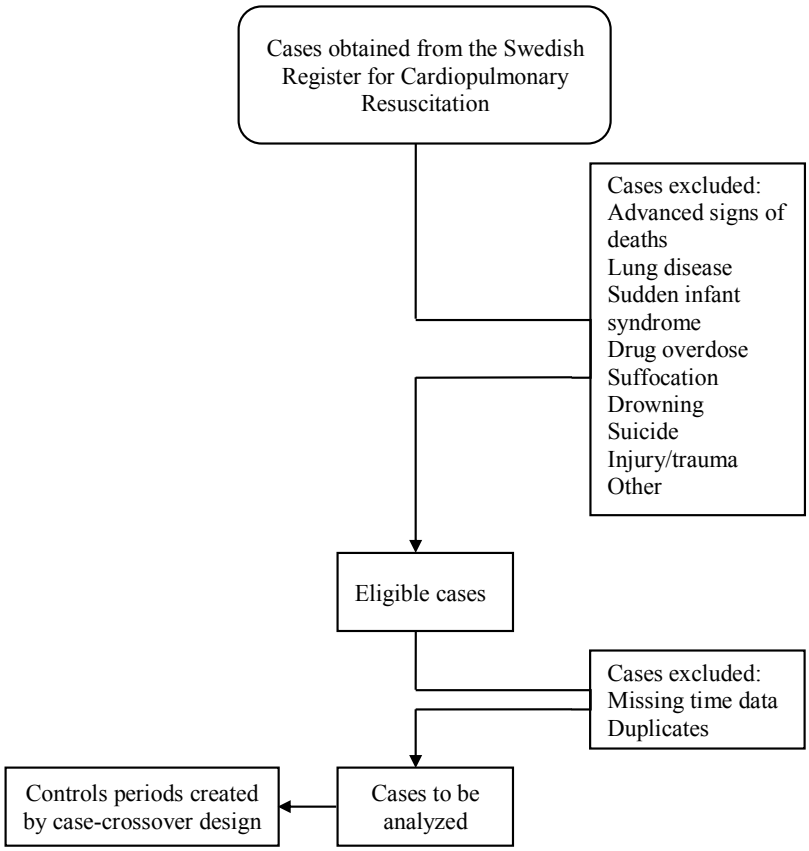

Figure 3.1 Flow chart demonstrating inclusion of out-of-hospital cardiac arrest cases

For Study IV, we also excluded cases for whom personal identification number was not available as personal identification numbers were required to link OHCA with their previous hospitalizations data.

3.1.3 Previous Hospitalizations

Data on all previous hospitalizations was obtained from The National Patient Register (NPR). Since 1987, NPR registers all in-patient care in Sweden and each hospitalization is linked to the personal identifications number. We obtained information on primary and secondary diagnosis, admission and discharge dates of previous hospitalization since 1987. We linked all deaths to previous hospitalizations to explore susceptibility to air pollution. We categorized individuals into different disease groups based on the principal diagnosis code (ICD-9 and ICD-10) at discharge.

In study I, we used hospitalizations five years prior to death to explore potentially susceptible groups. Susceptibility was based on previous hospitalizations for all cardiovascular diseases (CVD; ICD-9 codes 390–459, ICD-10 codes I00–I99). We further categorized all CVD into previous hospitalizations for i) acute myocardial infarction (AMI; ICD-9 code 410, ICD-10 codes I21 and I22); ii) heart failure (ICD-9 code 428, ICD-10 code I50); and ii) dysrhythmia (ICD-9 code 427, ICD-10 code I46–I49). Individuals with more than one hospitalization were

counted in different categories, thus, categories were not mutually exclusive. The temporal occurrences of previous hospitalizations with respect to successive death were grouped into three time intervals: 0–28 days, 29 days to 2 years, and 2 to 5 years before death. The same individual may have had different CVD diagnoses in each of the time intervals but contributed a maximum of one event for the same CVD diagnosis in each of the time interval.

In study II, we explored potentially susceptible groups based on hospitalization occurring three years preceding death. Individuals who had a cardiovascular cause of death were characterized into groups based on previous hospitalizations for i) AMI (ICD-9 410, ICD-10 I21-I22); ii), all other CVD (ICD-9 390-409, 411-459, ICD-10 I00-20, I23-99), excluding individuals with AMI; iii) respiratory diseases (ICD-9 460-519, ICD-10 J00-99), excluding individuals with prior hospitalizations for CVD; iv) diabetes (ICD-9 250, ICD-10 E10-14), excluding individuals with previous hospitalizations for CVD and respiratory diseases; v) other diseases, excluding individuals with CVD, respiratory diseases, and diabetes; vi) individuals with no hospitalization between 0-3 years before death for any disease but had earlier hospitalizations; and vii) individuals who had not been hospitalized since 1987. All previous hospitalization categories were mutually exclusive

For respiratory deaths, we categorized individuals based on previous hospitalizations for i) COPD (ICD-9 490-496, ICD-10 J40-47, J67); ii) pneumonia (ICD-9 480-486, ICD-10 J12-J18), excluding individuals with COPD; iii) other respiratory diseases (ICD-9 460-480, 486-490, 497-519, ICD-10 J00-11, J19-40, J48-66, J68-99), excluding individuals with previous hospitalizations for COPD and pneumonia; iv) any disease other than respiratory disease; v) individuals with no hospitalizations between 0-3 years but had earlier hospitalizations and vii) individuals with no record of previous hospitalizations since 1987. All previous hospitalization categories were mutually exclusive.

In Study IV, we naively explored whether previous hospitalization for any disease compared to no hospitalizations resulted in differences in associations between O_3 and OHCA. We then created indicator variables for previous hospitalizations for i) AMI (ICD-9 410, ICD-10 I21-I22); ii) heart failure (ICD-9 428, ICD-10 I50); iii) arrhythmias (ICD-9 426-427, ICD-10 I44-I49); iv) diabetes (ICD-9 250, ICD-10 E10-14); v) hypertension (ICD-9 401-405, ICD-10 I10-I15); and vi) stroke (ICD-9 430-438, ICD-10 I60-68). These variables were not mutually exclusive.

3.1.4 Air Pollution and Meteorological Parameters

Air pollutants we investigated in our studies were O_3, NO_2, NO_x, $PM_{2.5}$, PM_{10}, and coarse particles. Meteorological parameters used were temperature and relative humidity. All data on air pollutants, temperature and relative humidity for all studies was in hourly averages. Data for Stockholm County was obtained from a single urban background monitoring station located at Torkel Knutssonsgatan 20, approximately 20 m above ground-level, administered by Stockholm-Uppsala County Air Quality Management Associations. Measurements of NO_2, NO_X and O_3 began in 1990, PM_{10} in 1994 and $PM_{2.5}$ in the end of 1999. Therefore, in

studies I and II not all the pollutants are available throughout the study time period. Coarse particle fraction was calculated as the difference between PM_{10} and $PM_{2.5}$. For study I and II, calendar day 24-hour averages for NO_2, NO_X, $PM_{2.5}$ and PM_{10} were calculated. For O_3 we first generated 8-hour running averages from the hourly observations and from that we calculated the 8-hour daily maximum. The 8-hour maximum O_3 was missing on 8.3% of days during the study period and data was not imputed for the analysis. For the other pollutants, the missingness of 24-h averages range from 5.4 to 11.3% since measurements started.

For Study III, we used data from Torkel Knutssonsgatan for all air pollutants. Additional O_3 data was provided by the Swedish Environmental Research Institute from a countryside station Aspvreten, 80 km southwest of Stockholm. Hourly values were used to calculate running means for exposure windows. Data on meteorological variables were obtained from suburban station, 50 m high meteorological mast, located in Högdalen.

For study IV, air pollution and meteorological data for Gothenburg and Malmö was obtained from Department of Environment Management of both cities from 2006-2014. All the data was in hourly averages. Gothenburg's measuring station is located at Femman, approximately 25 m above the ground level. Measurements for $PM_{2.5}$ were only available for the years 2007-2010, while PM_{10} unavailable from October 2013 to the end of 2014 due to measuring problems with the instrument. The missingness of 2-h averages for $PM_{2.5}$, PM_{10}, NO_2, NO_x, and O_3 was 46 %, 16 %, 2 %, 2 %, and 11 %, respectively. Measuring station at Malmö is located at Rådhuset, the missingness of 2-h averages for $PM_{2.5}$, PM_{10}, NO_2, NO_x, and O_3 was 4 %, 3 %, 1.8 %, 24 %, and 1 %, respectively.

3.2 STATISTICAL METHODS AND ANALYSES

3.2.1 Studies I and II

3.2.1.1 Time-series

We used time-series study design for studies I and II. This design is used to evaluate a relationship between an exposure and an outcome variable. Both exposure and outcome are aggregated over the same time units during a specific time period. This design is used to study short-term changes in the health outcome followed by transient changes in exposure. Behavioral variables or personal characteristics are not considered potential confounders as these factors would not be associated or change with the unit of temporal change in environmental exposures [87]. Only confounding variables in time-series design are those with short-term temporal variability associated with the exposure and the outcome. Important confounders in air pollution studies are meteorological variables like temperature, seasonal or periodic patterns or long-term trends of both exposure and outcome. Day of week and holidays are also potential confounders [87].

Our studies were adjusted for seasonal patterns and long-term trends, relative humidity, temperature, daily influenza hospital admissions, public holidays and day of the week effect. In both studies I and II, day of the week and holidays were used as indicator variables. The

mean value of the relative humidity on the day of death and the preceding day before death (0-1 day) was modeled as a linear term and the mean value of the temperature during 0-1 day was modeled by cubic splines with 4 degrees of freedom (df) in study I, and in study II by restricted cubic splines with 2 df. In study I, a 7 day average of daily influenza admissions in Stockholm were modelled as a penalized spline with 4 df and as a restricted cubic spline with 2 df in study II. In study II, long-term time trend was modeled as linear and quadratic functions of the day number throughout the study period and seasonal periodicity was modeled using sine and cosine terms with wavelengths of 3, 6, 12, and 36 months.

3.2.1.2 Poisson regression

In study I and II, we used Poisson regression to assess the associations between air pollutants and the risk of total, cardiovascular, and respiratory mortality in those with and without previous hospitalizations. Poisson regression is a statistical method frequently used to model count data. The response variable i.e. outcome is in the form of event counts for example number of deaths while the explanatory variable can be continuous or a combination of continuous and categorical variables.

3.2.1.3 Statistical analyses

For study I, we used 0-1 day averages for all pollutants and for O_3 0-1 day average of 8-hr maximum was used.

We first analyzed single pollutant models and then performed stratified analysis according to previous hospitalizations for the pollutants that demonstrated associations with total mortality. We also conducted an interaction analysis between the individuals with AMI and individuals without AMI but with other CVD. We then performed two-pollutants models. We also performed stratified analysis by i) age categorized as 30-70, 71-84, and 85+, ii) seasons categorized cold (October to March) and warm (April to September) season, and iii) sex.

In study II, we used 0-1 and 0-6 day averages for all pollutants and for O_3 same averages are used but were constructed from 8-hr maximum. For relative humidity and temperature, we used 0-1 day averages.

We investigated associations between transient exposure to air pollution and cardiovascular mortality and respiratory mortality using lags 0-1 and 0-6 in single lag models. We used the lag structure that demonstrated strongest association for each respective outcome in further analyses.

We performed two-pollutant models for pollutants that demonstrated individual associations We then conducted stratified analyses of cardiovascular and respiratory mortality according to previous hospitalizations. Furthermore, we investigated difference in risk by sex, age, and seasons using interaction terms. Age was dichotomized by the median at the time of cause-specific death of individuals with respective previous hospitalisations. Season was divided into cold (October to March) and warm (April to September) season.

3.2.2 Studies III and IV

3.2.2.1 Case-crossover

In studies III and IV, the case-crossover analysis with time-stratified referent strategy was used to analyze the association between transient exposure to air pollution and OHCA. The case-crossover design was developed to study the effects of transient exposure on acute health outcomes. In this design, the period immediately preceding the event time is considered the case period and other specified time intervals other than the case period are the control periods. The advantage of case-crossover design is it allows the patients to serve as their own controls thus slowly changing personal characteristics are controlled for.

In studies III and IV, models were adjusted for relative humidity and temperature. We used the same averaging periods as for exposure, however, for 2-h air pollution averages we used 24-h averages. In study III, we modelled temperature as piece-wise linear spline with a knot at the temperature threshold (12 ^{o}C) that was observed as the 24-h temperature associated with the lowermost OR for OHCA [88]. In study IV, temperature was modelled as a restricted cubic spline with 2 df. Relative humidity was modelled as a linear term in both studies.

3.2.2.2 Conditional logistic regression

In studies III and IV, we used conditional logistic regression. This statistical method is mainly used when a study participant identified as a case regarding the particular condition, treatment, or attribute of a study is matched with study participants acting as controls without that condition, treatment, or attribute. This method is used to test the probability of an event to occur while controlling for other covariates.

3.2.2.3 Statistical analyses

In study III, we used 2-h, 24-h, and 72-h means as our exposure periods for all air pollutants and 8-h maximum O_3 was calculated within the previous 24-h.

We first analyzed associations between short-term exposure to air pollution and OHCAs using our three exposure windows. For pollutants that demonstrated associations we performed two-pollutant models. We performed seasonal analysis for cold (October to March) and warm (April to September) season. We modelled temperature as piece wise linear with a knot at the lowest risk temperature of 14 ^{o}C in winter and 10 ^{o}C in summer. We also investigated effect modification by sex and age by constructing multiplicative interaction terms. Age was categorised as below the median or above including median.

We performed an interaction analysis between 2-h exposure to air pollution and OHCA by event location under the assumption that exposure classification would perform better for events that occurred outdoors. Using information available for pick-up location of OHCA, we coded events as outdoors if they occurred in the street, taxis, cars, public transport, public transport terminals or stations, and in sports facilities. Furthermore, the events occurring at

home, workplace, health center, and nursing homes were coded as indoors. Cases for which the location of event was specified as other and unclear were coded as unknown. In addition to investigate the likelihood that witnessed OHCA would have a better temporal assessment of time of OHCA and affect our associations, we performed an interaction analysis using information on witnessed or unwitnessed cases.

For study IV, we used 2-h and 24-h averages and 8-h maximum O_3 was calculated in the same manner as in study III.

We included all OHCA that occurred within 100 km radius of the monitoring station. First, we performed analysis using 2-h and 24-h averages for all our air pollutants and limited our further analyses to the averaging period that demonstrated the clearest association in terms of a combination of the largest point estimate and narrowest CI. We then proceeded with two-pollutant models for pollutants that demonstrated individual effects. We explored difference in risk by i) age, dichotomized by median age at the time of OHCA; ii) sex; iii) seasons, categorized into cold (October to March) and warm (April to September) season; and vi) previous hospitalizations, dichotomized by previous hospitalizations, for instance for heart failure or no previous hospitalizations for heart failure. For all effect modification analyses we constructed multiplicative terms.

The estimates are expressed as percent increase or relative difference in risk of death or as odds ratios (OR) with 95% confidence intervals (CIs) per 10 $\mu g/m^3$ increase in air pollution levels. Data management, descriptive statistics and main analysis in study II, III, and IV were performed using Stata, while in study I statistical software R was used.

3.3 ETHICAL PERMITS

All studies have been approved by Regional Ethical Review Board. Reference number for studies I and II is 20091919-31/1 and for studies III and IV 2009/1524-32.

4 RESULTS

The studies included in this thesis investigated the role of previous hospitalizations on four outcomes i.e total mortality, cardiovascular mortality, respiratory mortality, and OHCA in relation to O_3 exposure. The first two studies were focused on total, cardiovascular, and respiratory mortality and last two studies were focused on OHCA, and results are presented following the same order.

4.1 SHORT-TERM EXPOSURE TO OZONE AND TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY IN INDIVIDUALS WITH AND WITHOUT PREVIOUS DISEASES

4.1.1 Study Populations

4.1.1.1 Total mortality

From 1990 to 2010, there were 302,283 total deaths in Stockholm County with an average of 39 deaths per day. Deaths in women were slightly more than half of the total deaths. Out of 196,916 individuals with previous hospitalizations for CVD, about 18 % individuals had previous hospitalizations for AMI and about 30 % individuals had previous hospitalizations for heart failure. There were around 10 % individuals with previous hospitalizations for dysrhythmia (Table 4.1).

4.1.1.2 Cardiovascular mortality

The average age at the time of death by cardiovascular disease was 77 years in men and 84 years in women. Fifteen percent had been previously hospitalized for AMI (Table 4.1). Among individuals that had not been previously hospitalized for AMI, hospitalization for other CVD constituted 44%. Four percent had prior admissions for respiratory diseases after excluding individuals with previous hospitalization for AMI and other CVD. Of the remaining individuals, <1% had previous hospitalizations for diabetes. Twelve percent of all cardiovascular deaths included individuals who had not been hospitalized for any disease during the 3 years immediately preceding death. Five percent of the individuals who died in CVD had never been admitted to hospital for any disease since the start of the inpatient registry in 1987 and were more likely to be men and on average younger than previously hospitalized participants.

Table 4.1 Characteristics and categorization of total (ICD-9 001-999; ICD-10 A00-U99), cardiovascular (ICD-9 390-459; ICD-10 I00-I99), and respiratory (ICD-9 460-519; ICD-10 J00-J99) deaths by previous admissions for diseases among Stockholm County residents ≥30 years old, 1990-2010

Categorization of mortality	Diagnosis of hospital admission		Total	Percent	Mean age (SD)	Female (%)
	ICD-9	ICD-10				
A. Total deaths			302,283		77 (12)	52
Individuals previously hospitalized for						
i) Any cardiovascular disease	390–459	I00–I99	196,916	100	80 (10)	50
ii) AMI	410	I21-I22	35,176	18	80 (9)	48
iii) Non-AMI			161,741	82	80 (10)	50
iv) Heart failure	428	I50	58,848	30	81 (9)	49
v) Dysrhythmia	427	I46, I49	20,557	10	80 (10)	51
B. Total cardiovascular deaths			136,624	100	81 (10)	54
Individuals previously hospitalized for						
i) AMI	410	I21-I22	20,948	15.0	81 (11)	47
ii) Non-AMI CVD	390-409, 411-459	I00-I20, I23-I99	60,346	44.2	81 (10)	55
iii) Respiratory diseases	460-519	J00-J99	5,919	4.4	81 (10)	51
iv) Diabetes	250	E10-E14	1,081	1.0	81 (10)	51
v) Other diseases	All except above	All except above	24,283	18.0	81 (10)	60
vi) Not hospitalized in 0-3 years*			16,190	12.0	83 (11)	58
vii) Not hospitalized since 1987			7,417	5.4	73 (13)	41
C. Total respiratory deaths			23,281	100	80 (10)	53
Individuals previously hospitalized for						
i) COPD	490-496	J40-J47, J67	5,774	25.0	80 (11)	53
ii) Pneumonia	480-486	J12-J18	6,003	26.0	79 (11)	46
iii) Other respiratory diseases	460-480, 486-490, 497-519	J00-J11, J19-J40, J48-J66, J68-J99	1,648	7.0	80 (11)	50

iv) Other diseases	All except above	All except above	6,774	29.0	79 (11)	56
v) Not hospitalized in 0-3 years*			2,442	10.0	84 (11)	66
vi) Not hospitalized since 1987			640	3.0	80 (14)	54

Note: All previous hospitalizations categories are mutually exclusive except for total death. *These individuals had hospitalizations between 1987 and 3 years preceding their death but not in the 3 years preceding death.

4.1.2 Exposure Characteristics

In Stockholm County, during our study period average levels of all measured pollutants were below WHO AQG. Ozone measurements demonstrated a near-normal distribution with sizable variability whereas other pollutants showed right-skewed distributions (Table 4.2)

Table 4.2 Distribution of air pollution concentrations and meteorological parameters in 2 day (lag 0-1) and 7 day average (lag 0-6), Stockholm, Sweden, 1990–2010

Parameters	2 day average				7 day average			
	Mean (SD)	Percentile		IQR	Mean (SD)	Percentile		IQR
		5th	95th			5th	95th	
O_3	62.8 (20)	31.3	97.1	27.7	62.7 (18)	34.0	93.4	27.0
$PM_{2.5}$	8.2 (5)	3.3	18.5	4.6	8.2 (4)	4.0	16.3	3.9
PM_{10}	15.3 (8)	6.4	32.3	8.8	15.3 (7)	7.7	29.3	7.4
NO_2	19.0 (9)	7.4	34.6	11.3	19.1 (7)	9.2	32.0	9.3
NO_x	26.9 (19)	8.4	60.3	18.3	27.1 (15)	11.0	54.0	16.3
Temp	7.6 (8)	-5	20.0	12.3	-	-	-	-
Rh	74.7 (12)	50.1	92.2	17.7	-	-	-	-

O_3, ozone, based on daily 8-hour max values; $PM_{2.5}$, mass concentration of particles ≤ 2.5 μm in aerodynamic diameter; PM_{10}, mass concentration of particles ≤ 10 μm in aerodynamic diameter; NO_x, nitrogen oxides; NO_2, nitrogen dioxide; Temp, temperature; Rh, relative humidity

4.1.3 Associations Between Ozone and Total Mortality

In study I, we observed that individuals with and without previous hospitalizations demonstrated a 0.5% higher mortality per 10 μg/m^3 increase in 0-1 day average of 8-hour maximum O_3 concentrations (Figure 4.1). In two-pollutant model, the association between O_3 and mortality became stronger on addition of NO_2, $PM_{2.5}$ and PM_{10} in the model, except for NO_x where the association remained similar (Figure 4.2).

Furthermore, individuals with previous hospitalizations for AMI demonstrated a stronger association (1.72% increased risk per 10 μg/m^3; 95% CI: 0.44%, 3.02%) between O_3 exposure and mortality, three times higher risk than for those with no previous hospitalizations for AMI. Moreover, O_3 in the warm season showed stronger associations with total mortality in these individuals (2.47%, 95% CI: 0.54%, 4.43%). However, individuals with previous hospitalizations for heart failure, dysrhythmia, and any other non-AMI CVD did not demonstrate an increased susceptibility to O_3 exposure in relation to total mortality (Figure 4.3).

We further categorized time lapse between hospitalizations for individuals with previous AMI hospitalizations and date of death to investigate the temporal influence of previous

hospitalizations on the risk of O_3-related death. We observed that hospitalizations for AMI from 29 days to two years before death was important in influencing the association between O_3 and total mortality compared to very recent (< 29 days before death) or older (> two years before death) previous AMI hospitalizations.

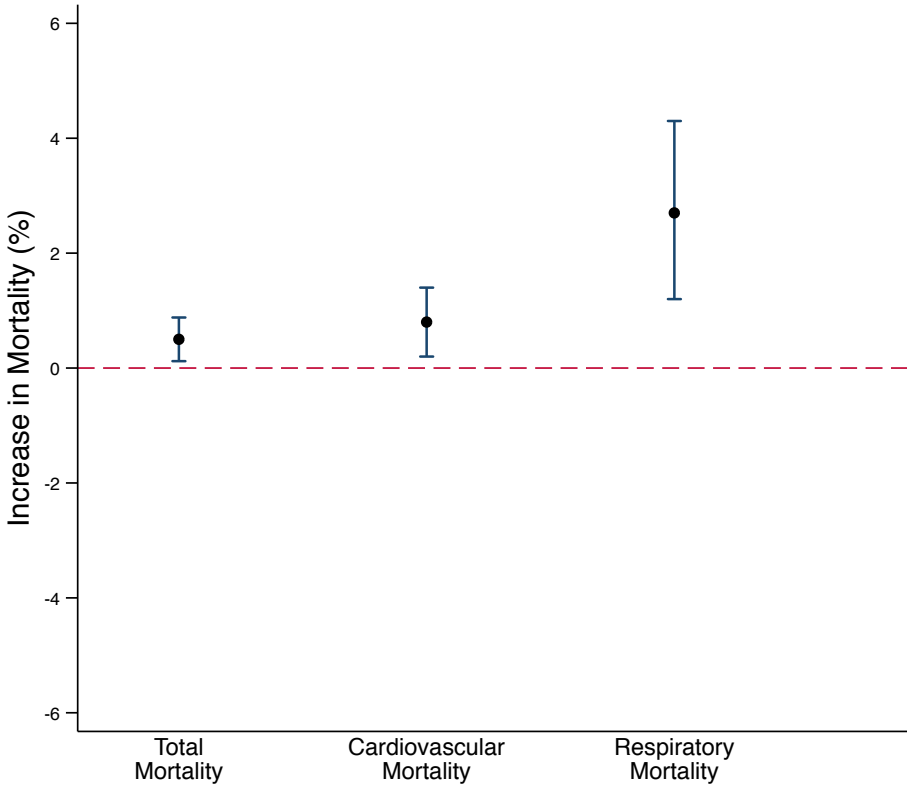

Figure 4.1 Percent change (95 % confidence interval) in total mortality, cardiovascular mortality, and respiratory mortality associated with a 10 μg/m^3 increase in 2 day, 2 day, and 7 day average of 8-hour maximum O_3 concentrations, respectively, Stockholm, 1990-2010

We observed a tendency of stronger associations between O_3 and total mortality in oldest age group of 85+ (2.1%, 95% CI: −0.0%,4.2%) compared with the middle age (71–85 years) category (1.1%, 95% CI: −0.73%, 3.0%). Furthermore, younger individuals (<71 years of age) also had an indication of higher risk (3.3%, 95% CI: 0.39%, 6.3%) of mortality following higher O_3 levels compared with the middle age category of individuals, however the difference was not significant.

We did not observe differences in O_3-related risk of total mortality between men (2.1%, 95% CI: 0.68%, 3.5%) and women (1.4%, 95% CI: −0.07%, 2.8%; interaction p-value = 0.4).

4.1.4 Associations Between Ozone and Cardiovascular Mortality

We observed associations between 8-h maximum O_3 levels and cardiovascular mortality for both averaging periods. Effect estimates were larger and confidence intervals were narrower for 2 day averaged 8-h maximum O_3 levels before death (0.8 % increased risk per 10 μg/m^3; 95% CI: 0.2%, 1.4%), in comparison with 7 day averaged exposure (Table 4.3). In two-

pollutant models, association between O_3 and cardiovascular mortality remained robust to the inclusions of NO_2, and NO_x in the model, while with $PM_{2.5}$ estimates became non-significant. With PM_{10} in the model, the estimate for O_3 became slightly stronger (1.0 % increased risk per 10 μg/m^3; 95% CI 0.3%, 1.7%) but an unexpectedly decrease in the risk of CV mortality related to PM_{10} (-1.2%; 95% CI: -2.3%, -0.1%, per 10 μg/m^3 increment) was observed (Figure 4.2).

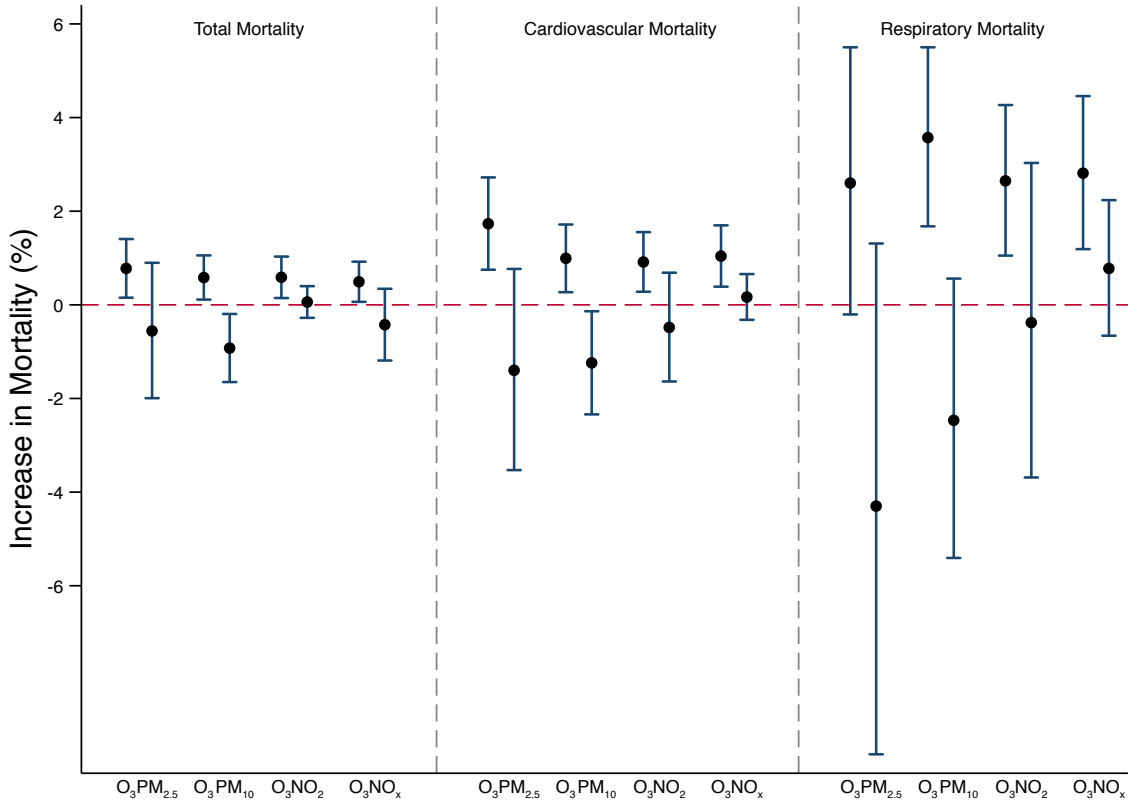

Figure 4.2 Percent change (95 % confidence interval) in total mortality, cardiovascular mortality, and respiratory mortality associated with a 10 μg/m^3 increase in 2 day, 2 day, and 7 day average of 8-hour maximum O_3 concentrations, respectively, in two-pollutant model

Individuals with previous AMI hospitalizations demonstrated 2.1% higher cardiovascular mortality (95% CI 0.51%, 3.8%) per 10 μg/m^3 increment of 0-1 day average 8-hr maximum O_3 (Figure 4.3). No significant associations were observed between O_3 exposure and cardiovascular death in individuals with prior hospitalizations for CVD excluding AMI, respiratory diseases, diabetes or any other disease. We observed associations between O_3 and cardiovascular deaths in individuals who had not been hospitalized between 0 to 3 years before cardiovascular death and who had never been hospitalized since 1987. The magnitudes of effect estimates were similar to individuals with prior AMI admissions for both of these categories of individuals.

Among individuals who had prior hospitalizations for AMI we observed a higher risk of cardiovascular death per 10 μg/m^3 increment of 0-1 day average 8-hr maximum O_3 in individuals older than the median age (82 years; 4.2%; 95% CI: 2.5%, 6.3%) compared with individuals equal to or below the median age (0.11%, CIs: -1.7%, 1.9%). We observed an indication of higher susceptibility in women (3.0%, CIs: 1.2%, 4.8%) compared to men (1.3%, CIs: -0.45%, 3.1%). Season did not seem to influence the association between O_3 exposure and cardiovascular mortality.

4.1.5 Associations Between Ozone and Respiratory Mortality

We observed a 2.7% higher risk of respiratory death per 10 μg/m^3 higher 0-6 day average O_3 levels (Figure 4.1). Estimates were lower for 0-1 day average O_3 and respiratory death (Table 4.3). In two-pollutant models in the co-presence of PM_{10}, NO_2, and NO_x, the association between O_3 exposure and respiratory mortality remained strong and significant (Figure 4.2). In a two-pollutant model including 0-6 lag O_3 and $PM_{2.5}$, we observed a weaker estimate (0.26%, 95% CI: -0.00%, 0.52%) for O_3 while the estimate for $PM_{2.5}$ did not change (-4.3%, 95% CI: -9.2%, 0.94 %).

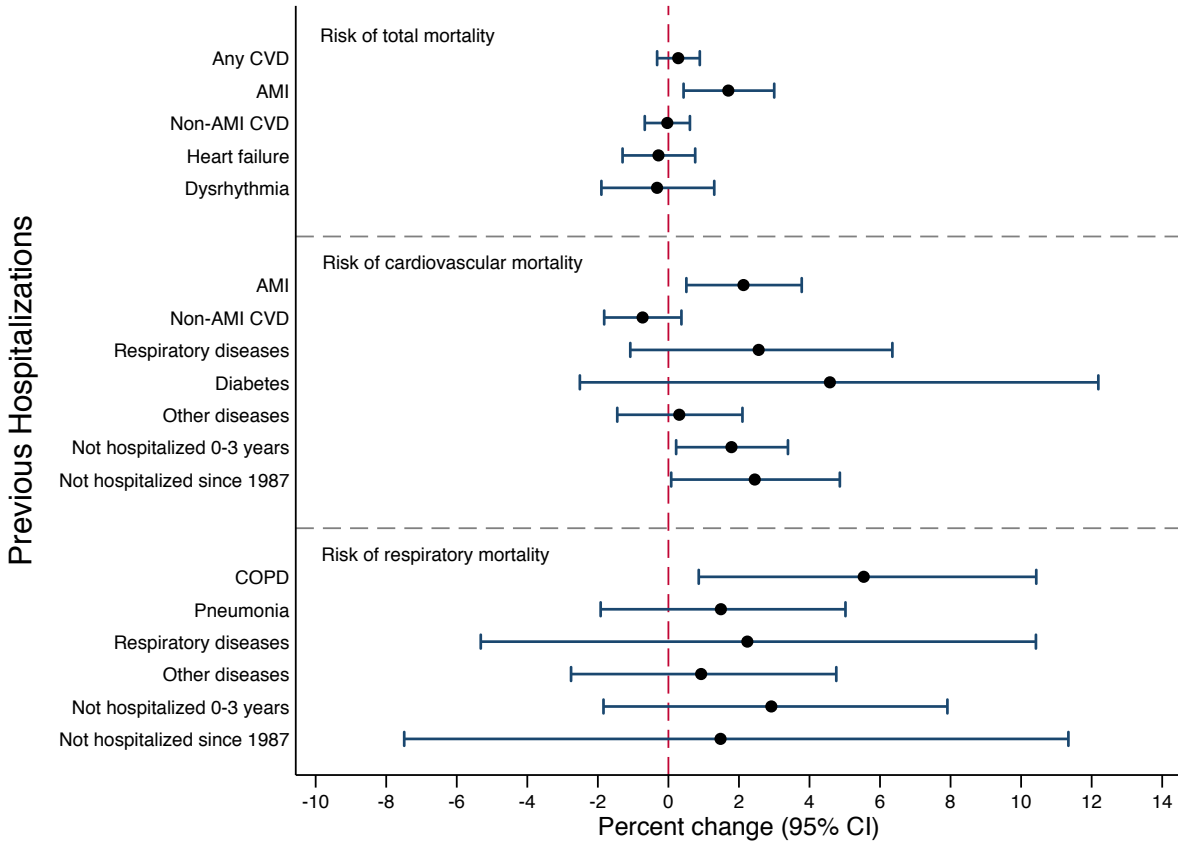

Figure 4.3 Percent change (95 % confidence interval) in total, cardiovascular, and respiratory mortality associated with a 10 μg/m^3 increase in 2 day, 2 day, and 7 day average of 8-hour maximum O_3 concentrations, respectively. Stratified by previous hospitalizations categories and absence of any hospitalization between 0 to 3 years, or since 1987. All strata are mutually exclusive except for total mortality.

The results of associations between 7 day O_3 and respiratory mortality by categories of hospitalization demonstrated positive associations (5.5% increased risk per 10 μg/m^3 95% CI: 0.9%, 10%) in individuals with previous COPD hospitalizations (Figure 4.3). We did not observe significant associations between O_3 exposure and respiratory death in individuals with prior hospitalizations for pneumonia, for respiratory diseases excluding COPD and pneumonia or for any other disease.

In further exploratory analyses associations between 7 day average O_3 and respiratory mortality in individuals with previous COPD hospitalizations remained unchanged in models including a multiplicative term for O_3 and sex, age, or season

4.1.6 Associations Between Other Pollutants and Total and Cardiorespiratory Mortality

No associations were observed between average $PM_{2.5}$, PM_{10}, NO_2, and NO_x levels and total, cardiovascular or respiratory mortality (Table 4.3).

Table 4.3 Percent change in cardiovascular and respiratory mortality in all subjects associated with a 10 μg/m^3 increase in 7 day and 2 day average 8-hour maximum O_3 concentrations, respectively.

Pollutant	Averaging period	Cardiovascular Mortality		Respiratory Mortality	
		Percent change	95 % CI	Percent change	95 % CI
O_3	01 day lag	0.8	(0.2, 1.4)	1.4	(0.06, 2.7)
	0-6 day lag	0.7	(0.02, 1.5)	2.7	(1.2, 4.3)
$PM_{2.5}$	01 day lag	-0.7	(-2.8, 1.5)	-0.2	(-4.3, 4.1)
	0-6 day lag	-1.2	(-3.8, 1.4)	-4.0	(-8.9, 1.1)
PM_{10}	01 day lag	-0.9	(-2.0, 0.2)	0.04	(-2.2, 2.3)
	0-6 day lag	-1.0	(-2.4, 0.4)	-0.8	(-3.6, 2.2)
NO_x	01 day lag	-0.1	(-0.5, 0.4)	0.3	(-0.6, 1.2)
	0-6 day lag	0.02	(-0.6, 0.7)	-0.1	(-1.5, 1.3)
NO_2	01 day lag	-0.7	(-1.8, 0.4)	0.3	(-2.1, 2.7)
	0-6 day lag	0.3	(-1.2, 1.8)	-0.1	(-4.4, 2.1)

O_3, ozone, based on daily 8-hour max values; $PM_{2.5}$, mass concentration of particles ≤ 2.5 μm in aerodynamic diameter; PM_{10}, mass concentration of particles ≤ 10 μm in aerodynamic diameter; NO_x, nitrogen oxides; NO_2, nitrogen dioxide

4.2 SHORT-TERM EXPOSURE TO OZONE AND OUT-OF-HOSPITAL CARDIAC ARREST: SUSCEPTIBILITY BY PREVIOUS DISEASES

4.2.1 Study Populations

In study III, we included 5,973 OHCA that occurred in Stockholm County from 2000 to 2010. A majority of OHCAs occurred in men (67%). The average age at the time of OHCA was 74 in women and 70 in men. About two-thirds of the OHCA occurred at home (Table 4.4).

The time period for study IV was from 2006 to 2014 and total of 11,923 EMS-assessed OHCAs were included from Stockholm County, Gothenburg, and Malmö. About 90% of the OHCAs occurred indoors. A majority of OHCAs occurred in men and the average age at the time of OHCAs in women was 69 years and 72 years in men. About 16% of the individuals had previous hospitalizations for AMI. Arrhythmias (24%), dominated by atrial fibrillation, were the most commonly occurring diagnoses of previous hospitalization in the individuals who had OHCA. Percentages of hospitalizations for stroke (2.5 %) and hypertension (3.3 %) were low. Individuals with previous hospitalizations were six percent. Forty-four percent of the individuals had been hospitalized due to any disease three or more times since 1987. There were 21% of the individuals who had no hospitalization for any disease before OHCA (Table 4.4).

Table 4.4 Descriptive statistics of out-of-hospital cardiac arrests in Stockholm County, 2000-2010 and pooled statistics for Stockholm, Gothenburg, and Malmö from 2006-2014

	Study Time period	Diagnosis of previous hospitalizations		Total	Mean Age	Female	Indoors
		ICD 9	ICD 10		(SD)	(%)	(%)
Out-of-hospital cardiac arrests	2000-2010			5,973	71 (15)	32	69
All Out-of-hospital cardiac arrest	2006-2014			11,923	70 (16)	34	90
Individuals with no hospitalization		-	-	2,552	65(18)	32	88
Individuals hospitalized for							
i) AMI		410	I21-I22	1,987	76 (11)	24	90
ii) Heart Failure		428	I50	1,611	778 (11)	30	92
iii) Arrhythmias		426 – 427	I44- I49	2,909	72 (14)	30	87
iv) Diabetes		250	E10-E14	682	70 (12)	31	92
vi) Hypertension		401-405	I10-I15	395	74 (13)	37	93
vii) Stroke		430-438	I60-I68	303	78 (12)	32	93

4.2.2 Exposure Characteristics

Air pollution levels were generally lower in Gothenburg and Stockholm compared to Malmö (Table 4.5). The difference in air pollution levels for 2 and 24-h case and control periods was very small in both study settings and time periods.

4.2.3 Associations Between Ozone and Out-of-Hospital Cardiac Arrest

In study III, we observed positive associations between O_3 and OHCAs in both 2- and 24-h averages, with a higher estimate for the latter (Figure 4.4). Study IV, confirmed this association (Table 4.5). Further in study III, in a distributed lag model for 24-h lags from lag-0 to lag-6, the lag-0 demonstrated an independent association between O_3 and OHCAs. For the cumulative 3 day average of O_3 exposure, we observed an OR of 1.05 (95% CI: 1.01, 1.09) for a 10 mg/m^3 increase. In two pollutant models, the association between O_3 and OHCA remained unchanged in the co-presence of particulate matter, while on addition of NO_2 in the model CIs spanned null.

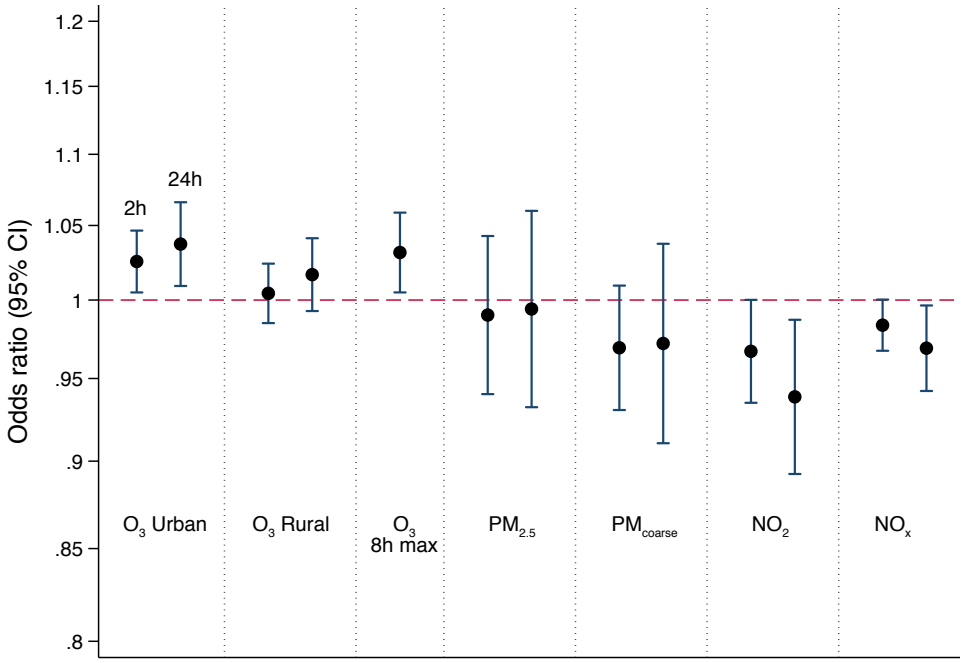

Figure 4.4 Associations of 2-hour and 24-hour exposure to air pollutants with OHCA per 10 µg/m^3 in Stockholm from 2000 to 2010, adjusted for temperature and relative humidity.

Our results demonstrated an indication of stronger associations in the cold season (OR: 1.05; CI: 1.01 – 1.10) compared with the warm season (OR: 1.01; CI: 0.97–1.05; interaction P-value = 0.1) in 24-h O_3 exposure window. We also performed analysis based on the location of OHCAs and observed stronger association between O_3 and OHCAs in events occurring outdoors (OR: 1.13; 95 % CI: 1.05 – 1.21) compared with the events that occurred indoors (OR: 1.02; 95 % CI: 0.99 – 1.05) for 2-h exposure. In interaction analyses by age, gender, or witnessed events we did not observe differences in association between 24-h average O_3 levels and OHCA (age = 0.9, interaction P-value; gender = 0.4, witnessed = 0.4)

Table 4.5. City-specific distribution of 2 and 24-h means for air pollution levels and meteorological parameters during 2006-2014

City	Study Time Period	Parameter ($\mu g/m^3$)		Mean (SD)	Percentiles 5th	Percentiles 95th	IQR	Mean for cases (SD)	Mean for controls (SD)
Stockholm	2000-2010								
		$PM_{2.5}$	24-h	8.1 (5)	3.0	19.1	4.8	7.9 (5)	7.9 (8)
		PM_{coarse}	24-h	7.2 (6)	1.5	20.2	5.3	7.2 (6)	7.2 (6.3)
		NO_2	24-h	15.7 (8)	5.5	30.2	9.7	15.4 (8)	15.5 (8)
		NO_x	24-h	20.2 (14)	6.3	43.8	13.0	19.6 (13)	19.9 (14)
		O_3 (rural)	24-h	60.0 (19)	29.2	91.6	26.4	59.2 (19)	58.7 (19)
		O_3 (urban)	24-h	51.2 (19)	20.4	81.2	26.2	50.5 (18)	49.9 (18)
		O_3urban 8hr-max	24-h	62.2 (20)	29.2	96.1	27.4	61.3 (20)	60.8 (20)
		Temp	24-h	7.1 (8)	- 5.6	19.3	12.5	6.4 (8)	6.6 (8)
		Rh	24-h	77.0 (12)	52.7	93.1	17.9	77.1 (13)	77.3 (13)
Stockholm	**2006-2014**								
		O_3							
			2-h	50.9 (22)	14.6	86.3	29.5	50.3 (22)	50.1 (22)
			24-h	50.9 (18)	22.0	80.0	24.8	50.8 (18)	50.7 (18)
			8-h max	61.7 (19)	30.5	93.1	26.7	61.3 (19)	61.2 (19)
		$PM_{2.5}$							
			2-h	6.5 (6)	0.4	17.2	5.1	6.2 (6)	6.2 (5)
			24-h	6.3 (5)	1.3	15.5	4.3	5.9 (5)	5.9 (5)
		PM_{10}							
			2-h	14.3 (11)	3.6	34.5	10.1	14.6 (11)	14.9 (11)
			24-h	14.3 (8)	5.5	30.6	8.5	14.0 (8)	14.1 (8)
		NO_2							
				13.1 (11)	2.0	35.4	12.2	14.0 (12)	14.1 (12)

			13.1 (7)	3.8	27.6	9.1	13.0 (8)	13.0 (8)
		Temp	24-h	7.2 (8)	-5.9	19.4	12.5	6.6 (8)	6.7 (8)
		Rh	24-h	76.7 (14)	49.5	96.6	20.8	77.8 (14)	77.7 (14)
Gothenburg	**2006-2014**								
		O_3							
			2-h	50.2 (26)	5.1	91.1	35.4	50.6 (26)	50.3 (26)
			24-h	50.1 (20)	16.8	82.3	27.0	50.7 (21)	50.5 (21)
			8-h max	63.8 (22)	27.3	99.5	28.1	64.3 (23)	64.1 (22)
		$PM_{2.5}$							
			2-h	7.8 (5)	1.4	18.1	5.7	7.6 (5)	7.7 (5)
			24-h	7.7 (4)	2.9	15.7	4.6	7.5 (4)	7.4 (4)
		PM_{10}							
			2-h	16.6 (12)	3.8	37.5	11.7	16.9 (12)	16.8 (12)
			24-h	16.5 (8)	6.7	31.9	8.61	16.2 (8)	16.2 (8)
		NO_2							
			2-h	23.1 (17)	5.4	57.5	18.8	23.5 (17)	23.6 (18)
			24-h	23.1 (12)	8.6	46.6	14.4	22.8 (12)	22.9 (12)
		Temp	24-h	9.2 (7)	-3.3	20.0	11.1	8.7 (7)	8.8 (7)
		Rh	24-h	77.3 (13)	52.8	96.4	17.5	76.2 (12)	74.6 (16)
Malmö	**2006-2014**								
		O_3							
			2-h	53.8 (22)	15.2	88.4	29.3	54.0 (22)	53.7 (23)
			24-h	53.7 (18)	21.8	81.8	24.9	54.3 (18)	54.2 (19)
			8-h max	64.4 (20)	30.2	96.9	25.2	65.0 (20)	64.8 (20)
		$PM_{2.5}$							
			2-h	12.0 (9)	2.6	30.4	8.8	12.2 (10)	12.2 (10)
			24-h	12.0 (8)	3.5	28.0	7.8	12.1 (9)	12.1 (9)
		PM_{10}							
			2-h	17.0 (10)	5.2	37.3	10.9	17.5 (11)	17.6 (11)
			24-h	17.0 (9)	7.1	34.7	9.1	17.3 (10)	17.4 (10)

NO_2							
	2-h	17.2 (11)	5.5	38.3	12.3	17.9 (11)	18.0 (11)
	24-h	17.2 (8)	7.6	32.1	10.0	17.2 (11)	17.2 (8)
Temp	24-h	9.6 (7)	-2.1	20.2	11.1	8.9 (7)	9.0 (7)
Rh	24-h	74.6 (11.2)	53.7	90.11	16.3	75.2 (11.0)	75.1 (11.0)

O_3, ozone; $PM_{2.5}$, mass concentration of particles ≤ 2.5 μm in aerodynamic diameter; PM_{10}, mass concentration of particles ≤ 10 μm in aerodynamic diameter; NO_2, nitrogen dioxide: Temp, temperature; Rh, relative humidity

4.2.4 Other Pollutants

Neither in study III nor in study IV were associations observed between $PM_{2.5}$, PM_{10}, coarse particles, NO_2, and NO_x and OHCAs in all exposure averages (Figure 4.4 and Table 4.6).

Table 4.6. Pooled Analysis. Associations of 2-h and 24-h exposure to air pollutants with out-of-hospital cardiac arrest from 2006-2014, per 10 μg/m^3

Pollutant (μg/m^3)	Moving average (h)	OR	95% CI
O_3	2-h	1.02	(1.00, 1.03)
	24-h	1.02	(1.00, 1.04)
	8-h max	1.01	(1.00, 1.03)
$PM_{2.5}$	2-h	0.97	(0.94, 1.01)
	24-h	0. 97	(0.93, 1.01)
PM_{10}	2-h	0.99	(0.96, 1.01)
	24-h	0.96	(0.93, 0.99)
NO_2	2-h	0.98	(0.96, 0.99)
	24-h	0.97	(0.94, 1.00)

O_3, ozone; $PM_{2.5}$, mass concentration of particles ≤ 2.5 μm in aerodynamic diameter; PM_{10}, mass concentration of particles ≤ 10 μm in aerodynamic diameter; NO_2, nitrogen dioxide:

4.2.5 Susceptibility to Ozone-Related Risk of OHCA by Previous Diseases

We did not observe any difference in higher 2-h average O_3 exposure and the risk of OHCA between individuals with or without previous hospitalizations for any disease based on the p-value for interaction and strata specific results (Figure 4.5). In addition, we did not observe a difference in risk of OHCA following 2-h average O_3 exposure in individuals hospitalized for any of the pre-specified diagnoses of AMI, heart failure, diabetes, hypertension or stroke (all p-values for interaction > 0.05) except for arrhythmias where we found evidence of interaction. Common for all strata-specific results, ORs for individuals with previous hospitalizations were below or near the null whereas the comparison group reflected results found in the overall study population. In the case of individuals previously hospitalized for arrhythmias, results indicated a counter-intuitively lower risk of OHCA with higher exposure to O_3.

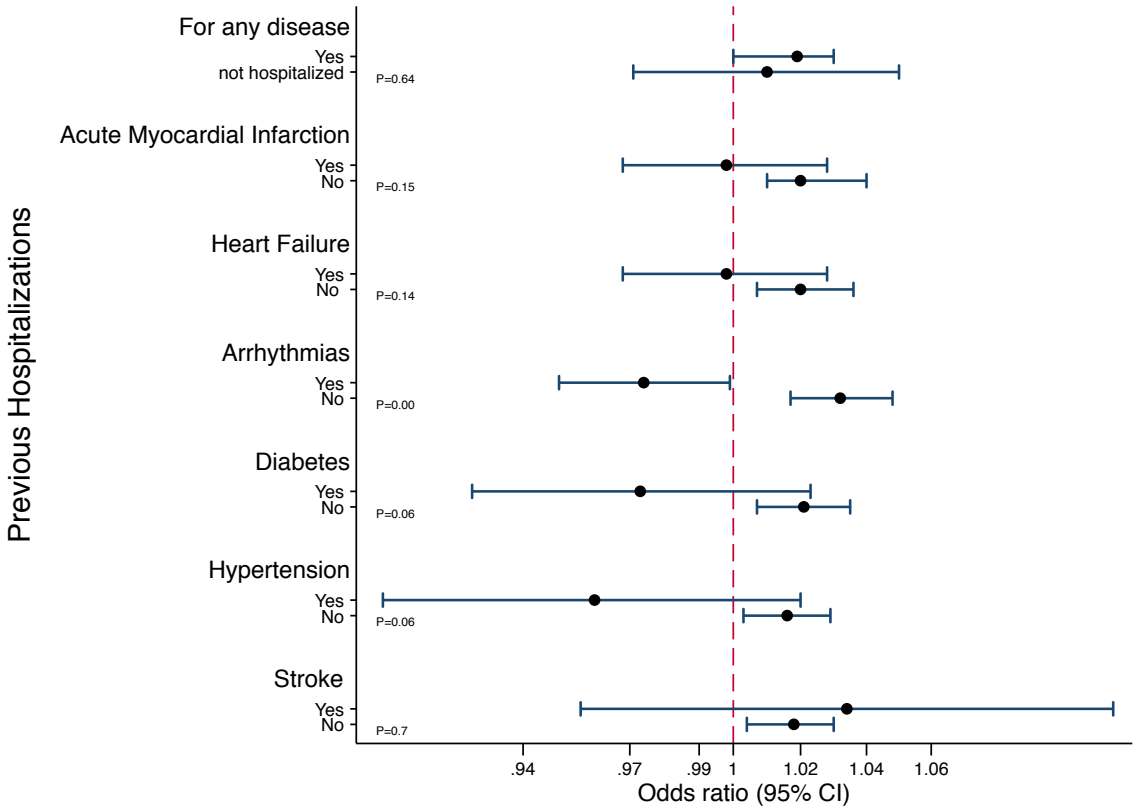

Figure 4.5 Pooled Analysis. Odds ratios for out-of-hospital cardiac arrest per 10 μg/m^3 higher 2-hour average of O_3 concentrations by previous hospitalizations for any disease, acute myocardial infarction, heart failure, arrhythmias, diabetes, hypertension, and stroke.

5 DISCUSSION

We observed associations between short-term exposure to elevated urban background O_3 concentrations and the increased risk of total, cardiovascular and respiratory mortality and OHCA. Individuals who had been previously hospitalized for acute myocardial infarction had an increased risk of O_3-related mortality, both total and cardiovascular, in comparison to overall population. Higher O_3-related risk of cardiovascular mortality was also observed in individuals with out-of-hospital cardiovascular death as their first manifestation of an underlying disease. Furthermore, individuals who had previous hospitalizations for COPD had an increased risk of O_3-related respiratory mortality. However, we did not observe previous diseases to confer susceptibility to higher O_3 levels and the risk of OHCA.

5.1 OZONE EXPOSURE AND MORTALITY

This thesis adds to the existing literature demonstrating associations between transient O_3 exposure and total mortality as well as with cardiovascular mortality and respiratory mortality. Our results of association between O_3 exposure and total mortality are consistent with the large meta-analyses [72, 89] performed on the US and non-US cities which reported a 20 $\mu g/m^3$ increase of daily O_3 at 2 day average increased the risk of death by 0.87% (95% CIs, 0.55%, 1.18%). The Air Pollution and Health a European Approach (APHEA2) project consisting of 23 European cities also observed increase in total deaths per 10 $\mu g/m^3$ increase in the 1-hour O_3 concentrations (0.3%, 95% CIs: 0.17-0.52) and similar estimates were observed for 8-h maximum O_3. Similarly, several single [63, 90] and multicity studies [33, 91-97], and meta-analyses [72, 98] within and outside Europe have reported consistent significant associations between O_3 and cardiovascular mortality. On the contrary, respiratory mortality has been inconsistently associated with O_3 in all year analysis but stronger consistent significant associations were reported during the warm period of the year [63, 90, 93, 94, 98].

For cardiovascular mortality, we observed similar associations in both averaging periods (2 day and 7 day) of 8-hr maximum O_3. In contrast, higher estimates were observed for the association between 7 day average 8-hr maximum O_3 and respiratory mortality compared to the shorter averaging period of 2 day. This pattern is largely consistent with the APHEA study that also reported stronger estimates for the association between O_3 and respiratory mortality in longer lags (0-20 day) as compared to shorter lags (0 and 0-1 day), while the opposite was observed for cardiovascular mortality [93]. This implies that exposure to high O_3 levels has a more immediate effect on triggering cardiovascular mortality, whereas the effect on respiratory mortality might require longer O_3 exposure and other biological processes [93].

5.1.1 Risk with Previous Hospitalizations

5.1.1.1 Acute myocardial infarction

Some research has been conducted on identifying individuals susceptible to the harmful effects of O_3 based on previous CVD, however, our results are generally concordant with results from the existing studies. In our study I [24], we observed higher risk of death in association with 8-hr maximum O_3 exposure in individuals with previous AMI compared to the full study population. In study II, where we investigated cardiovascular mortality, we observed higher risk estimates than in study I (1,7% vs 2.1%) in individuals with previous hospitalizations for AMI that may be in part be explained by a more specific outcome. A study from Italy [33], investigating total mortality, reported non-significant associations between 0-5 day 8-hr maximum O_3 and total mortality in individuals with previous AMI hospitalizations (2.6% increase risk per 10 $\mu g/m^3$ (95% CIs: -1.0%, 6.4%). Another study from Italy [69] investigating a more specific outcome, reported a borderline significant association between O_3 exposure and out-of-hospital coronary deaths in individuals who had previous hospitalizations for ischemic heart disease, which lends some support to our finding of increased susceptibility to cardiovascular mortality in individuals with previous hospitalizations for AMI. In contrast to our results, a large multicity study from the US using secondary cause of death as a proxy for pre-existing disease reported no increased susceptibility between O_3 and mortality for atherosclerotic conditions, however additional susceptibility was observed for atrial fibrillation [70].

5.1.1.2 Heart failure

In our study, we did not observe associations between O_3 exposure and total mortality in individuals with previous hospitalizations for heart failure. Other studies were also unable to report conferred susceptibility by previous hospitalization for heart failure for O_3-related risk of death [33, 69, 70]. A plausible explanation for the absence of association could be that these individuals are elderly and might have multiple comorbidities, which limits their outdoor movement and physical activity, leading to more time spent indoors and less exposure to O_3.

5.1.1.3 Diabetes

Previous studies have suggested diabetes as a susceptible condition for air pollution-related cardiovascular events [50, 99], and a study from Italy [33] reported diabetes as the pre-existing condition that conferred susceptibility to O_3-associated mortality. Results of other studies, including our study, point the same direction but with poor precision [69, 70].

5.1.1.4 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease, is a progressive irreversible airflow limitation and chronic inflammation of the lungs, and is the fourth leading cause of death worldwide [100]. The disease represents heavy economic burden and costs are largely associated with disease exacerbations which lead to emergency department visits, hospitalizations, and death. Ozone

exposure has been consistently associated with respiratory mortality in previous studies [63, 90, 93, 94, 98]. Studies include several large multi-city studies, and associations have generally been reported from exposure periods between 0-1 and 0-5 day lags, and our estimate of 2.7 higher risk per 10 $\mu g/m^3$ 0-6 day exposure is roughly in line with previously reported estimates. In addition to studies investigating O_3 exposure and respiratory mortality, several studies have observed associations between O_3 exposure and hospital admission for COPD [79-81, 101, 102]. Few previous studies have investigated the role of previous hospitalizations for respiratory diseases on association between O_3 exposure and respiratory mortality. None of these have reported increased risk of death in individuals with previous respiratory hospitalizations [33, 69, 70]. In our further exploratory analyses of these individuals with previous hospitalizations for COPD, we observed no evidence to support different susceptibility to O_3 by age and sex. Also, our seasonal analyses did not demonstrate influence of seasons on association between O_3 and respiratory mortality in individuals with COPD, while the previous studies have demonstrated stronger associations for the warm period of the year between O_3 exposure and respiratory mortality [29, 33, 93, 94] irrespective of previous hospitalizations.

5.1.2 Risk without Previous Hospitalizations

Out-of-hospital cardiovascular deaths with no previous hospitalization for any causes demonstrated a strong association with O_3 exposure. It is likely that many of these individuals had underlying condition that made them susceptible to O_3 exposure, but that this condition had not been subject to hospital care. General practitioner visits were not available as a possible indication of previous disease in our material. Epidemiological studies as well as autopsy series reported presence of structural heart disease, including coronary artery disease, in 50-95% of adults who suffered sudden cardiac death without previously known heart disease [103, 104]. Cardiovascular death in individuals not hospitalized since 1987 were relatively younger (mean age 73 years) compared to the rest of the individuals. Younger individuals are more likely to be exposed to higher O_3 levels through outdoor physical activity. These results lead to study III where we hypothesized that exposure to higher short-term O_3 levels increase the risk of OHCA [105].

5.2 OZONE AND OUT-OF-HOSPITAL CARDIAC ARREST

The results of our study demonstrated associations between transient exposure to O_3 and OHCA in a smaller sample from Stockholm [105] and in a large pooled dataset from Gothenburg, Malmö, and Stockholm. These results are consistent with some [49, 73-75] but not all studies [42, 44, 48, 82-85, 106]. Other studies have also observed independent associations of both O_3 and $PM_{2.5}$ with OHCA [44, 49, 75, 105] in contrast to our study where we did not observe associations for $PM_{2.5}$. Our results indicated a near instantaneous association of O_3 exposure with OHCA and were robust to the inclusion of PM_{10} or $PM_{2.5}$, suggesting independent associations of O_3 with OHCA. Studies from Houston, Helsinki, and France have also investigated short averaging time windows for exposure [73-75]. However, only our study and the Houston study reported associations between O_3 exposure and OHCA

in hourly averages while others reported delayed effects. The magnitude of our associations between 24-hr average O_3 and risk of OHCA are in line with results from a recently published meta-analysis (OR of 1.01; 95% CIs: 1.00,1.02 versus our result OR 1.02; 95% CIs:1.00, 1.04 per 10 $\mu g/m^3$) [107].

5.2.1 Susceptibility by Previous Hospitalizations to Ozone-Related OHCA

Pre-existing conditions such as diabetes and cardiovascular diseases including myocardial infarction, heart failure, diabetes, hypertension, rhythm disorders and stroke have been associated with increased risk of OHCA [108-110]. A study on out-of-hospital coronary events [69] reported higher risks of events following higher O_3 levels, in individuals with previous hospitalizations for cerebrovascular diseases and artery diseases. Previous studies [48, 49] reported higher susceptibility to OHCA following $PM_{2.5}$ exposure in individuals with previous disease history for diabetes, hypertension, and stroke. However, previously no study has investigated the possible effect modification of the association between O_3 and OHCA by previous manifestation of cardiovascular disease.

Our study did not demonstrate previous hospitalizations conferring susceptibility to O_3 exposure in relation to OHCA. Indeed, we observed no difference in risk of OHCA on exposure to O_3 between individuals with or without previous hospitalization for any disease and we did not observe any higher risk among individuals previously hospitalized for AMI, heart failure, arrhythmias, diabetes, hypertension or stroke. Some of the discrepancies between our study and other studies [24, 33, 69] are likely explained by different outcomes investigated (although some overlap is expected), the temporal resolution of the event or exposure, or model specifications between time-series and case-crossover design. Furthermore, differences in O_3 estimates between different studies partly reflect variations in total O_3 exposure resulting from the variations in the amount of outdoor O_3 permeating indoors [111], and the amount of time spent indoors [112]. Ozone is highly reactive and removed by indoor surfaces [113], therefore, measures based on outdoor monitors may be an inadequate marker of capturing personal O_3 exposure [78]. In Sweden, buildings are comparatively tight with limited air exchange rates, which keeps the median indoor O_3 levels around 10 $\mu g/m^3$ [114], remarkably lower than mean outdoor O_3 levels (median 51 $\mu g/m^3$).

Furthermore, it is plausible that individuals with the same underlying condition in different populations might have different medical treatment and management, which turn may confer differences in their risk from ambient air pollution. There are however no epidemiological or clinical studies to support this argument [115].

5.3 EFFECT MODIFICATION BY AGE AND SEX

5.3.1 Difference in Risk of Ozone-Related Death in Individuals with Previous AMI Hospitalization

We identified elderly with previous AMI hospitalizations as high-risk groups in both studies I and II. Elderly have been consistently reported as susceptible to the detrimental effects of O_3 exposure [24, 33, 57, 69]. In contrast, findings on O_3 related mortality risk difference by sex are inconsistent. We observed a tendency of higher risk of cardiovascular mortality in women with previously hospitalizations for AMI, consistent with a majority of studies that have reported stronger associations between O_3 exposure and cardiovascular outcomes in women [33, 70], although some inconsistencies remain [24] and studies investigating specific pathophysiological mechanisms are lacking [70].

5.3.2 Difference in Risk of OHCA

We did not observe risk differences by age and sex. In contrast, other studies have consistently reported elderly as susceptible to harmful effects of O_3 exposure on OHCA [49, 74, 76]. Comparatively, differences in associations between O_3 and OHCA by sex are inconsistent [73-76, 105].

5.4 SEASONAL INFLUENCE OF OZONE

Ozone has a high temporal variation with peaks on sunny days during the spring and summer in Sweden. Indoor sources of O_3 are very few and due to its highly reactive nature it reacts with the indoor surface which further reduces indoor O_3 exposure, in particular during the heating season when Swedish houses tend to be more closed. Thus, O_3 exposure mostly occurs outdoors only, especially in the winter period. A majority of studies have reported higher risks of O_3-related total, cardiovascular, and respiratory mortality in summer seasons [27, 33, 70, 93, 94], however, in our studies we did not observe a clear influence of seasons on risk of death in individuals with previous AMI hospitalizations.

Furthermore, among studies investigating associations between OHCA and air pollution exposure only one study from Houston reported stronger associations during the warm season [73] whereas other studies either reported no difference [75, 76, 105] or an indication of higher risks during cold season [49, 75]. We may speculate that study-specific differences in seasonal results may reflect behavioral differences related to climate and time spent indoors.

5.5 POSSIBLE BIOLOGICAL MECHANISMS

Inflammation and oxidative stress are integral components in the pathogenic process of COPD [116] but also in that of atherosclerotic heart disease [117]. Ozone has a high oxidative potential and produce respiratory inflammation that may hinder recovery from infections, or may generate systemic responses. Animal studies have shown that O_3 adversely react with airway epithelium, inducing smooth muscle hyperplasia and dysfunction, and to contribute to subsequent bronchial hyperresponsiveness [118]. Panel studies on healthy

young individuals observed that O_3 exposure was associated with increase in levels of inflammatory markers such as pro-inflammatory cytokines and C-reactive protein, plasminogen activator inhibitor 1, fibrinogen, and 8-hydroxy-2′-deoxyguanosine, reduced lung function, and decreased heart rate variability [119-122]. Ozone exposure has also been associated with alterations in the autonomic nervous system [77, 123-126] and changes in blood pressure in individuals with [127] and without [128] previous cardiovascular disease. Several other mechanisms, like arterial pressure control, coagulation, thrombosis, vascular tone, and oxidative stress have also been associated with O_3 exposure [57, 128] supporting a likely association with cardiovascular mortality. Furthermore, these association were observed soon before the measurement consistent with the effects of O_3 on mortality largely in few days of exposure [93].

5.6 METHODOLOGICAL CONSIDERATIONS

In epidemiology, research often relies on data collected for other purposes and even if collected for your particular study aim, it is unlikely to be free of errors. People live complicated lives and epidemiologists need to reduce that complexity, and thus no epidemiological study can be free of errors. The challenge is to carry out a study with an aim to minimize error to the greatest extent possible and be able to assess the effects of unavoidable errors. An important aspect of epidemiology is to be able to recognize likely sources of errors and, essentially, to assess the potential effects of those errors on your work [129]. In the following sections I discussed the challenges we faced while performing studies included in this thesis.

5.6.1 Exposure Assessment

The aim of short-term exposure assessment in air pollution studies is to obtain an exposure estimate as representative as possible to the true individual air pollution exposure. The ideal situation would be to measure personal exposure which represents exposure outdoors and indoors; however, it is impractical for large studies with rare events like mortality. Instead time-series of continuous exposure measurements from strategically located fixed air pollution monitoring stations are used. Similar to other studies of ambient air pollution we relied on data from fixed monitors in each city to estimate exposure instead of individual monitoring of air pollution exposure. We had a high coverage of hourly measurements of air pollution data minimizing the risk of temporal misclassification. In study IV, we restricted our study areas to 100 km radius of monitoring station and further restriction to 50 km in sensitivity analyses resulted in similar results for all pollutants. The underlying assumption is that variability in short-term individual exposure in part is described by the variability of the concentrations at the fixed monitoring sites. In Stockholm County we have one regional and several local monitoring stations and all pollutant measurements from all stations were highly correlated and exhibited temporal compared to spatial variability in short-exposure windows (Figure 5.1 and Figure 5.2).

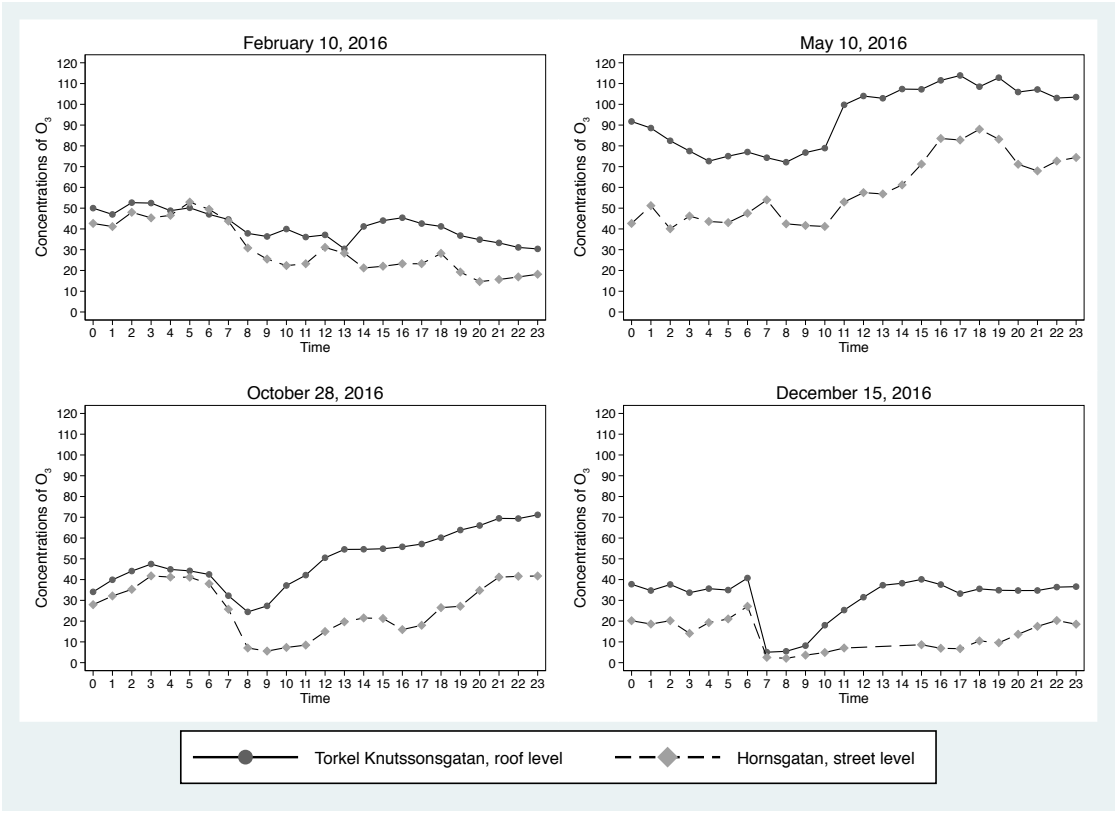

Figure 5.1 Hourly O_3 concentrations on randomly selected days in the same year from regional and local monitoring stations in Stockholm County

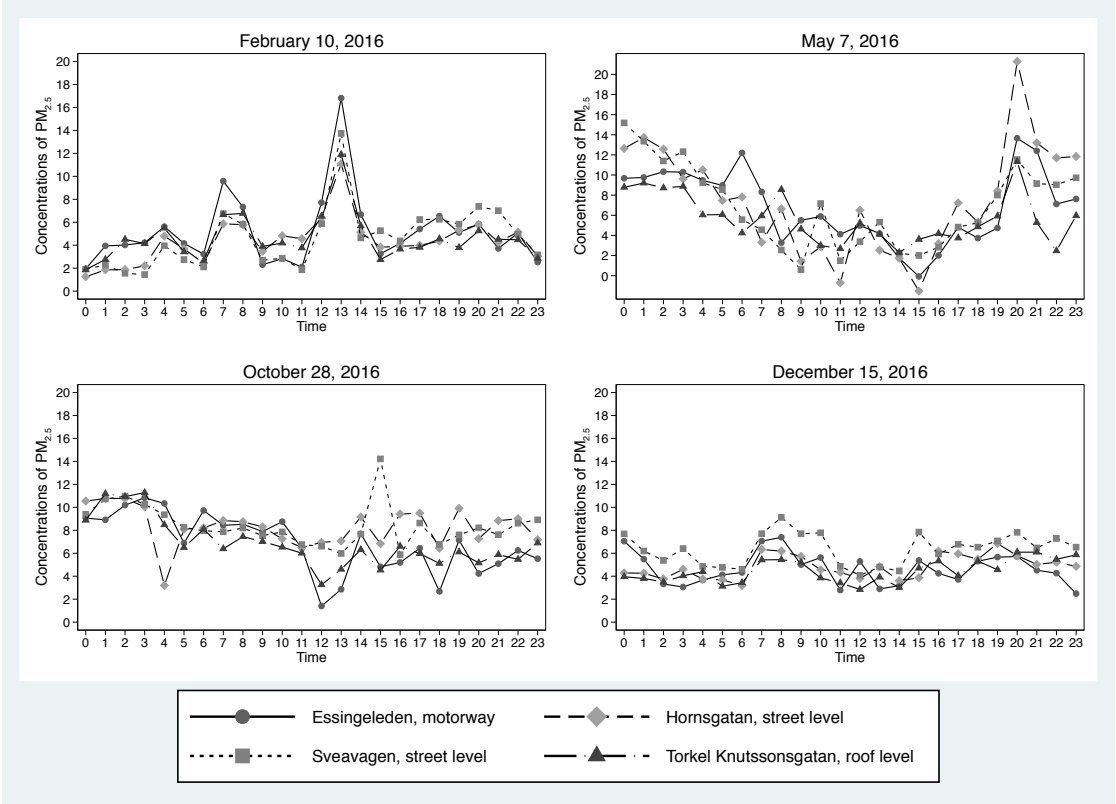

Figure 5.2 Hourly $PM_{2.5}$ concentrations on randomly selected days in the same year from regional and local monitoring stations in Stockholm County

Data on long-term exposure to O_3 was not available, furthermore, we did not have a data regarding time spent indoors, activity pattern, and location of residents, that could decrease the exposure misclassification; however, this type of misclassification is likely non-differential and therefore underestimate observed associations [130]. However, we cannot exclude some bias.

5.6.2 Outcome Assessment

All outcome data for all our studies were collected from registers. The quality of register data is dependent on the physician's assigned diagnosis. Furthermore, the accuracy of diagnosis will depend to some extent on the disease manifestation and varies with primary and secondary diagnoses. For instance, diagnosis for AMI and stroke is slightly more precise in the Swedish hospital discharge register than for heart failure [131]. In addition, heart failure as a primary diagnosis has a validity of 95% vs 75% when listed as a secondary cause of hospitalization [131].

The strength of the Swedish Cause of Death and Inpatient registries is their full coverage and high validity [132]. As discussed earlier some level of inaccuracy is expected in the registry data, it is not, however, expected to vary with our exposure and thus the net result would be an underestimation of the observed estimates.

We benefitted from a large sample of a well-defined outcome with etiologic data of OHCA and highly accurate information concerning handling times provided by Swedish Register for Cardiopulmonary Resuscitation [133]. The wide-coverage of the register also reduced the risk of selection bias.

5.6.3 Confounding Control

The research question addressed in studies I and II was whether short-term variation in O_3 levels was related to mortality. Our exposure and outcome data have seasonal patterns as well as long-term trends and day of week effects. It is necessary to control for these potentially joint temporal patterns in order to separate them from short-term associations between O_3 exposure and mortality [134]. We went through a rigorous process of selecting statistical models for confounding control of seasonal patterns and long-term trends with the aim to arrive at a bias-free model to estimate associations. Generally in epidemiology age, sex, biomass index, socioeconomic status, smoking status, and so on, are common confounders but these confounders are not applicable in our studies as they do not fluctuate on daily basis and therefore cannot be associated with variations neither in ambient O_3 levels nor in short-term variations in mortality risk. Potential confounders in short-term air pollution studies are entities with short-term fluctuations and possible relations to short-term changes in O_3 and mortality [134]. Ozone and temperature are strongly correlated and temperature has been associated with mortality [135] and also exacerbate physiological responses to short-term exposure to O_3 [136]. Therefore, appropriate control for temperature while assessing

effects of O_3 is crucial. In our study setting, O_3 and temperature were moderately correlated. We adjusted our final models using restricted cubic spline with 4 df, allowing a high degree of flexibility. We performed several analyses using 2 day, 7 day, and 14 day for temperature adjustments and we also excluded 99^{th} and 95^{th} percentiles but nothing affected our results, indicating that the confounding control in our final model was adequate.

In studies III and IV, we used a time stratified case-crossover study design [137]. This design allows cases to serve their own controls, thus, time invariant individuals characteristics are taken care of by the design (as in time-series analysis with Poisson regression). We selected controls periods on same time of the day, same day of the month, and within the same calendar month which allows the design to control for day of week effects, seasonal patterns, and to some extent long-term time trends. The potential confounders which vary over time are meteorological parameters like temperature and relative humidity. The confounding control for these two variables included adding temperature as piece-wise linear spline in Study III and as restricted cubic splines with 2 df in study IV and relative humidity was added as a linear term in both studies.

In comparison, case-crossover is easy to implement and seasonal patterns and long-term trends in both exposure and outcome are controlled by the design, while time-series requires intensive model specifications [138]. Both designs can give equitable estimates of the risk of detrimental health outcomes associated with transient exposure to higher levels of ambient O_3. Both designs, depending on choice of temporal smoothing in time-series design and selection of controls in case-crossover design, can be implemented in several different ways [138]. However, time-series design is more powerful compared to case-crossover in the sense that air pollution exposure on the day of event is compared with the exposure every other day in the study period but in case-crossover each case period is compared to a limited number of controls periods [139], in our case three or four. Therefore, the estimates based on time-series analysis are more precise [138].

5.6.4 Mortality Displacement

Mortality displacement is a concept to describe the possibility that deaths associated with exposure, for instance to O_3, occur mostly in individuals who are terminally ill and hence the effect of O_3 is merely to trigger the death slightly ahead of time [93]. In this case, positive associations between exposure and daily mortality on days with higher exposure are followed by negative associations between exposure and daily mortality on following days with similar orders of magnitude [93, 140]. Based on the mortality displacement hypothesis the public health significance of short-term air pollution studies has been questioned. A study investigating mortality displacement in the association of O_3 and mortality in 48 US cities did not observe mortality displacement in response to O_3, but rather concluded single day exposure averages may underestimate the public health impact of O_3 [93]. However, 21 European cities study, APHEA-2, reported an indication of displacement in total and cardiovascular mortality, but not for respiratory mortality [94]. In our studies, we did not specifically investigate short-term mortality displacement, but we found no evidence of

mortality displacement in the time span of 7 days, as estimates for 7 day and 2 day averages were similar.

5.6.5 Mortality or Case-Only Data

Death or mortality records are the oldest and widely used indicators of health status. Death has the advantage of its universality and that in most countries there are strong incentives for the authorities to accurately record who dies and when. However, mortality is an incomplete measure of health status because it does not consider chronic disease or disease burden and only measures the end of disease processes. Furthermore, the cause of death is difficult to accurately ascertain and becomes more complicated in case of multiple chronic diseases [141]. Our studies included case-only designs for mortality and OHCA and thus precluded any interpretation of disease incidence, as well as difference in mortality and OHCA incidence between different parts of the population.

5.7 PUBLIC HEALTH SIGNIFICANCE

Our findings indicate that individuals with previous history of myocardial infarction and chronic obstructive pulmonary disease are especially sensitive to O_3 exposure. These results support the consideration of increased risk in large susceptible subpopulations in health impact assessments of O_3 exposure. In Sweden, O_3 concentrations are greatly influenced by regional and intercontinental transport of O_3 and its precursors. Therefore, increased protection of public health requires mitigation efforts not only at a local but at a regional scale. For a more immediate increase in protections of the general public, forecasting and reporting real-time O_3 levels, involving media, with precautionary recommended measures may be developed. Furthermore, health care providers communicate with at-risk patients and precautionary recommendations may limit the health hazards of elevated O_3 levels. These measures at a local level are practical and feasible and may help to decrease exposure to O_3 and lower the associated respiratory and cardiovascular risk.

6 CONCLUSIONS

Ozone exposure was associated with increased risk of acute mortality and cardiac arrest in a Nordic environment with ~ 60 μg/m^3 annual 8-h maximum O_3 levels and individuals with previous disease manifestations showed higher O_3-related risks.

More specifically:

- Exposure to ambient O_3 was associated with increased risk of total, cardiovascular, and respiratory mortality within 2-7 days.
- Previous hospitalization for acute myocardial infarction was associated with an increased susceptibility for O_3-related total and cardiovascular death.
- Previous hospitalization for chronic obstructive pulmonary disease was associated with an increased susceptibility for O_3-related respiratory death.
- Exposure to ambient O_3 was associated with increased risk of out-of-hospital cardiac arrest within 2-72 hours but we did not demonstrate higher risks among individuals previously hospitalized for cardiovascular disease.

7 POPULAR SCIENCE SUMMARY

7.1 IN SWEDISH

Luften som vi andas innehåller luftföroreningar från naturligt förekommande källor såväl som från olika mänskliga aktiviteter (antropogena källor). Dessa föroreningar är gaser eller partiklar som företrädelsevis är så små att de är osynliga för blotta ögat. Naturligt förekommande källor inkluderar bland annat vulkanutbrott och olika typer av bränder medan de antropogena källorna inkluderar trafik, industri och förbränning av olika bränslen. Forskare över hela världen har studerat de negativa effekterna, efter både lång och kort tids exponering, av dessa föroreningar på människors hälsa och har observerat effekter på hjärt-kärlsjukdomar, lungsjukdomar, allergier och till och med på död.

I min avhandling har jag fokuserat på korttidseffekter av en gasformig luftförorening som heter ozon. Högt upp i atmosfären finns det ett ozonlager som hjälper till att skydda oss från ultraviolett strålning, men jag har studerat ozon vid marknivå. Det marknära ozonet skapas av kemiska reaktioner som involverar lättflyktiga organiska föreningar, som exempelvis metan, i närvaro av solljus. Kväveoxider är också involverade i dessa reaktioner. Ozon som skapats i en region kan färdas tusentals kilometer och bidra till förhöjda nivåerna långt ifrån där det skapats. Flera studier har rapporterat effekter av korttidsexponering för ozon på ökad dödlighet, liksom effekter på hjärtstopp utanför sjukhus och flertalet andra sjukdomar. Den samlade kunskapen om vilka i en befolkning som har en ökad risk att drabbas av negativa hälsoeffekter relaterade till ozon är knapphändig. Det är viktigt att identifiera känsliga grupper i befolkningen för att kunna skapa luftkvalitetsstandarder och riktlinjer som också skyddar viktiga känsliga grupper. Med tanke på detta var vår målsättning i den här avhandlingen att undersöka vilken roll tidigare sjukdomar har i att påverka den ozon-relaterade risken för dödlighet överlag, för död i hjärt-kärlsjukdom och för död i lungsjukdomar, liksom för risken att drabbas av hjärtstopp utanför sjukhus. För att genomföra vår studie inhämtade vi information om samtliga naturliga dödsfall som inträffade i Stockholms län mellan 1990 och 2010. Information om alla hjärtstopp utanför sjukhus som blev bedömda av sjukvårdspersonal inhämtades från det nationella hjärtstoppsregistret. Vi inkluderade alla hjärtstopp utanför sjukhus som inträffade i Stockholms län mellan 2006 och 2014, samt alla hjärtstopp utanför sjukhus som inträffade mellan 2006 och 2014 i Göteborg och Malmö. Med hjälp av personnumret sammanlänkade vi alla dödsfall och hjärtstopp utanför sjukhus med tidigare sjukhusinläggningar som registrerats i nationella patientregistret. Information om ozonnivåer inhämtades från en mätstation centralt placerad ovan tak i varje stad. Vi genomförde sedan en statistisk analys för att utvärdera effekten av ozonnivåer på totaldödlighet, hjärt-kärldödlighet och lungdödlighet, samt på hjärtstopp utanför sjukhus.

Våra resultat visade att individer som tidigare varit sjukhusvårdade på grund av en hjärtinfarkt eller en allvarlig lungsjukdom hade högre risk att dö jämfört med befolkningen i övrigt, efter 2 till 7 dagars exponering av förhöjda nivåer av ozon. I motsatts till detta verkade

inte tidigare sjukhusvård för hjärt-kärlsjukdomar påverka effekten av kortidsexponering för ökade ozonnivåer och risken för att drabbas av hjärtstopp utanför sjukhus.

Dessa resultat ger ytterligare stöd till tanken att det finns stora grupper i befolkningen som är särskilt känsliga för hälsopåverkan av ozon. I Sverige påverkas ozonnivåerna mycket av regional och interkontinental transport av ozon och de föreningar som bidrar till att ozon bildas. Det är därför av vikt att insattser för att förbättra folkhälsan genom minskade utsläpp av luftföroreningar inte bara sker på en lokal nivå utan också på en regional nivå. För att uppnå en mer direkt skyddande effekt av den generella befolkningen är det möjligt att utveckla verktyg i form av prognoser och realtidsrapportering av ozonnivåer som kan komma befolkningen till del genom media. Det är också möjligt att utveckla försiktighetsrekommendationer för känsliga grupper. Vidare kan vårdgivares kommunikation med patienter med en förhöjd risk och förebyggande rekommendationer begränsa de skadliga hälsoeffekterna av förhöjda nivåer av ozon. Dessa åtgärder på en lokal nivå är praktiska och genomförbara och kan hjälpa till att minska exponeringen för ozon och minska de relaterade riskerna för lungsjukdomar och hjärt-kärlsjukdomar.

7.2 IN ENGLISH

The air we breathe contains air pollutants from natural and man-made sources. These pollutants are gaseous or particles that mostly are so small that they are invisible to naked eye. Natural sources include volcanic eruptions and natural fires while the man-made sources include traffic, industry, and burning of fuels. Researchers around the globe have studied the negative effects, both long-term and short-term, of these pollutants on human health and have observed effects on cardiovascular diseases, respiratory illnesses, allergies, and even death.

In my thesis, I have focused on short-term effects of a gaseous air pollutant called ozone. Very high up there is an ozone layer that helps protect us from ultraviolet radiation, but I have studied the ozone at ground level. Such ozone is formed by chemical reactions involving volatile organic compounds, for example methane, in the presence of sunlight. Nitrogen oxides are also involved in these reactions. Ozone formed in one region can travel thousands of kilometer to contribute to increased levels far away. Several studies have reported effects of short-term ozone exposure on mortality, as well as with out-of-hospital cardiac arrest and other disease manifestations. Knowledge on whom among the general population is at higher risk of adverse ozone-related health effects is scarce. It is important to identify sensitive populations in order to provide guidelines for air quality standards that also protect significant sensitive groups within the general population. Therefore, in this thesis we aimed to explore the role of previous diseases in modifying the risk of mortality for all diseases, cardiovascular diseases, and respiratory diseases, as well as the risk of out-of-hospital cardiac arrests. To carry out our study we obtained a data on all natural deaths that occurred in Stockholm County from 1990 to 2010. Data on all out-of-hospital cardiac arrests which were assessed by emergency staff were obtained from the Swedish Register for Cardiopulmonary Resuscitation. We included all out-of-hospital cardiac arrests that occurred in Stockholm County from 2000 to 2010, as well as all out-of-hospital cardiac arrest that occurred from

2006 to 2014 in Stockholm, Gothenburg and Malmö. We used personal identification numbers to link all deaths and out-of-hospital cardiac arrests to their previous hospitalizations as recorded in the National Patient Register. Data on ozone was obtained from a single monitoring station in each city. We then performed statistical analyses on our data to assess effects of ozone levels on total, cardiovascular and respiratory deaths, and OHCA.

Our results showed that individuals who have been previously hospitalized due to a heart attack or to severe lung diseases are at a higher risk of death as compared to general population after 2 to 7 days exposure to increased ozone levels. In contrast, previous hospitalizations for cardiovascular diseases did not appear to change the effect of short-term exposure to elevated ozone concentrations on the risk out-of-hospital cardiac arrest.

These results support the consideration of increased risk in large susceptible subpopulations in health impact assessments of ozone exposure. In Sweden, ozone concentrations are greatly influenced by regional and intercontinental transport of ozone and its precursors. Therefore, increased protection of public health requires mitigation efforts not only at a local but at a regional scale. For a more immediate increase in protections of the general public, forecasting and reporting real-time ozone levels, involving media, with precautionary recommended measures may be developed. Furthermore, health care providers communicate with at-risk patients and precautionary recommendations may limit the health hazards of elevated ozone levels. These measures at a local level are practical and feasible and may help to decrease exposure to ozone and lower the associated respiratory and cardiovascular risk.

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9 REFERENCES

1. Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A: The contribution of outdoor air pollution sources to premature mortality on a global scale. *Nature* 2015, 525(7569):367-371.

2. Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA: Particulate matter air pollution and cardiovascular disease an update to the scientific statement from the American Heart Association. *Circulation* 2010, 121(21):2331-2378.

3. Nichols M, Townsend N, Scarborough P, Rayner M: Cardiovascular disease in Europe 2014: epidemiological update. *European heart journal* 2014, 35(42):2950-2959.

4. Forsberg B, Hansson H-C, Johansson C, Areskoug H, Persson K, Järvholm B: Comparative health impact assessment of local and regional particulate air pollutants in Scandinavia. *AMBIO: A Journal of the Human Environment* 2005, 34(1):11-19.

5. Chen TM, Gokhale J, Shofer S, Kuschner WG: Outdoor air pollution: ozone health effects. *Am J Med Sci* 2007, 333(4):244-248.

6. Andersson C, Alpfjord H, Robertson L, Karlsson PE, Engardt M: Reanalysis of and attribution to near-surface ozone concentrations in Sweden during 1990–2013. *Atmos Chem Phys* 2017, 17:13869-13890.

7. Derwent RG, Utembe SR, Jenkin ME, Shallcross DE: Tropospheric ozone production regions and the intercontinental origins of surface ozone over Europe. *Atmospheric Environment* 2015, 112:216-224.

8. Derwent RG, Stevenson DS, Collins WJ, Johnson CE: Intercontinental transport and the origins of the ozone observed at surface sites in Europe. *Atmospheric Environment* 2004, 38(13):1891-1901.

9. Montzka S, Reimann S, Engel A, Kruger K, Sturges W, Blake D, Dorf M, Fraser P, Froidevaux L, Jucks K: Scientific assessment of ozone depletion: 2010. *Global Ozone Research and Monitoring Project-Report No 51* 2011.

10. Guerreiro C: Air quality in Europe: 2013 report. 2013.

11. Li Q, Jacob DJ, Bey I, Palmer PI, Duncan BN, Field BD, Martin RV, Fiore AM, Yantosca RM, Parrish DD: Transatlantic transport of pollution and its effects on surface ozone in Europe and North America. *Journal of Geophysical Research: Atmospheres* 2002, 107(D13).

12. Querol X, Alastuey A, Pandolfi M, Reche C, Perez N, Minguillon MC, Moreno T, Viana M, Escudero M, Orio A *et al*: 2001-2012 trends on air quality in Spain. *Sci Total Environ* 2014, 490:957-969.

13. Bach H, Brandt J, Christensen JH, Ellermann T, Geels C, Hertel O, Massling A, Nielsen HØ, Nielsen O-K, Nordstrøm C: Services to assess the reasons for non-compliance of ozone target value set by Directive 2008/50/EC and potential for air quality improvements in relation to ozone pollution. 2014.

14. Cristina G: Air Quality in Europe: 2015 Report. In.; 2017.

15. Lövblad G, Henningsson E, Sjöberg K, Brorström-Lundén E, Lindskog A, Munthe J: Trends in Swedish background air 1980–2000. *EMEP Assessment Part II National Contributions* 2004:211-220.

16. Tang L, Karlsson PE, Gu Y, Chen D, Grennfelt P: Synoptic weather types and long-range transport patterns for ozone precursors during high-ozone events in Southern Sweden. *AMBIO: A Journal of the Human Environment* 2009, 38(8):459-465.

17. Bazhanov V, Rodhe H: Tropospheric ozone at the Swedish mountain site Åreskutan: Budget and trends. *Journal of atmospheric chemistry* 1997, 28(1):61-76.

18. Jönsson O, Andersson C, Forsberg B, Johansson C: Air pollution episodes in Stockholm regional background air due to sources in Europe and their effects on human population. *Boreal environment research* 2013, 18(3-4):280-302.

19. Adams M, Barrett K, Leeuw Fd, Pulles T: Air pollution in Europe 1990-2000. 2004.

20. Guerreiro C, de Leeuw F, Foltescu V: Air quality in Europe-2013 report. 2013.

21. Omstedt G, Andersson S, Asker C, Jones J, Kindell S: Luftkvaliteten i Sverige år 2020.

22. Organization WH, UNAIDS: Air quality guidelines: global update 2005: World Health Organization; 2006.

23. Halonen JI, Lanki T, Tiittanen P, Niemi JV, Loh M, Pekkanen J: Ozone and cause-specific cardiorespiratory morbidity and mortality. *J Epidemiol Community Health* 2010, 64(9):814-820.

24. Bero Bedada G, Raza A, Forsberg B, Lind T, Ljungman P, Pershagen G, Bellander T: Short-term Exposure to Ozone and Mortality in Subjects With and Without Previous Cardiovascular Disease. *Epidemiology (Cambridge, Mass)* 2016, 27(5):663-669.

25. Organization WH: Review of evidence on health aspects of air pollution-REVIHAAP Project. *Copenhagen: World Health Organization Regional Office for Europe* 2013.

26. Touloumi G, Katsouyanni K, Zmirou D, Schwartz J, Spix C, de Leon AP, Tobias A, Quennel P, Rabczenko D, Bacharova L *et al*: Short-term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. Air Pollution and Health: a European Approach. *Am J Epidemiol* 1997, 146(2):177-185.

27. Gryparis A, Forsberg B, Katsouyanni K, Analitis A, Touloumi G, Schwartz J, Samoli E, Medina S, Anderson HR, Niciu EM *et al*: Acute effects of ozone on mortality from the "air pollution and health: a European approach" project. *Am J Respir Crit Care Med* 2004, 170(10):1080-1087.

28. Dominici F, McDermott A, Daniels M, Zeger SL, Samet JM: Revised analysis of the National Morbidity, Mortality, and Air Pollution Study, Part II. *Revised Analyses of Time-Series Studies of Air Pollution and Health* 2003:5-24.

29. Peng RD, Samoli E, Pham L, Dominici F, Touloumi G, Ramsay T, Burnett RT, Krewski D, Le Tertre A, Cohen A *et al*: Acute effects of ambient ozone on mortality in Europe and North America: results from the APHENA study. *Air Qual Atmos Health* 2013, 6(2):445-453.

30. Katsouyanni K, Samet JM, Anderson HR, Atkinson R, Le Tertre A, Medina S, Samoli E, Touloumi G, Burnett RT, Krewski D *et al*: Air pollution and health: A

European and North American approach (APHENA). In. Boston, MA: Health Effects Institute; 2009: 5-90.

31. Zanobetti A, Schwartz J: Mortality displacement in the association of ozone with mortality: An analysis of 48 cities in the United States. *American Journal of Respiratory and Critical Care Medicine* 2008, 177(2):184-189.

32. Samoli E, Zanobetti A, Schwartz J, Atkinson R, Le Tertre A, Schindler C, Pérez L, Cadum E, Pekkanen J, Paldy A *et al*: The temporal pattern of mortality responses to ambient ozone in the APHEA project. *Journal of Epidemiology and Community Health* 2009, 63(12):960-966.

33. Stafoggia M, Forastiere F, Faustini A, Biggeri A, Bisanti L, Cadum E, Cernigliaro A, Mallone S, Pandolfi P, Serinelli M *et al*: Susceptibility factors to ozone-related mortality: a population-based case-crossover analysis. *Am J Respir Crit Care Med* 2010, 182(3):376-384.

34. Wong CM, Vichit-Vadakan N, Vajanapoom N, Ostro B, Thach TQ, Chau PY, Chan EK, Chung RY, Ou CQ, Yang L *et al*: Part 5. Public health and air pollution in Asia (PAPA): A combined analysis of four studies of air pollution and mortality. In., vol. 154. Boston, MA: Health Effects Institute; 2010: 377-418.

35. Axelsson C, Claesson A, Engdahl J, Herlitz J, Hollenberg J, Lindqvist J, Rosenqvist M, Svensson L: Outcome after out-of-hospital cardiac arrest witnessed by EMS: changes over time and factors of importance for outcome in Sweden. *Resuscitation* 2012, 83(10):1253-1258.

36. Ensor KB, Raun LH, Persse D: A case-crossover analysis of out-of-hospital cardiac arrest and air pollution. *Circulation* 2013, 127(11):1192-1199.

37. Levy D, Sheppard L, Checkoway H, Kaufman J, Lumley T, Koenig J, Siscovick D: A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. *Epidemiology* 2001, 12(2):193-199.

38. Rosenthal FS, Carney JP, Olinger ML: Out-of-hospital cardiac arrest and airborne fine particulate matter: a case-crossover analysis of emergency medical services data in Indianapolis, Indiana. *Environ Health Perspect* 2008, 116(5):631-636.

39. Silverman RA, Ito K, Freese J, Kaufman BJ, De Claro D, Braun J, Prezant DJ: Association of ambient fine particles with out-of-hospital cardiac arrests in New York City. *Am J Epidemiol* 2010, 172(8):917-923.

40. Sullivan J, Ishikawa N, Sheppard L, Siscovick D, Checkoway H, Kaufman J: Exposure to ambient fine particulate matter and primary cardiac arrest among persons with and without clinically recognized heart disease. *Am J Epidemiol* 2003, 157(6):501-509.

41. Rosenthal FS, Kuisma M, Lanki T, Hussein T, Boyd J, Halonen JI, Pekkanen J: Association of ozone and particulate air pollution with out-of-hospital cardiac arrest in Helsinki, Finland: evidence for two different etiologies. *J Expo Sci Environ Epidemiol* 2013, 23(3):281-288.

42. Wichmann J, Folke F, Torp-Pedersen C, Lippert F, Ketzel M, Ellermann T, Loft S: Out-of-hospital cardiac arrests and outdoor air pollution exposure in Copenhagen, Denmark. *PLoS One* 2013, 8(1):e53684.

43. Raza A, Bellander T, Bero-Bedada G, Dahlquist M, Hollenberg J, Jonsson M, Lind T, Rosenqvist M, Svensson L, Ljungman PL: Short-term effects of air pollution on out-of-hospital cardiac arrest in Stockholm. *Eur Heart J* 2014, 35(13):861-868.

44. Dennekamp M, Akram M, Abramson MJ, Tonkin A, Sim MR, Fridman M, Erbas B: Outdoor air pollution as a trigger for out-of-hospital cardiac arrests. *Epidemiology* 2010, 21(4):494-500.

45. Straney L, Finn J, Dennekamp M, Bremner A, Tonkin A, Jacobs I: Evaluating the impact of air pollution on the incidence of out-of-hospital cardiac arrest in the Perth Metropolitan Region: 2000-2010. *J Epidemiol Community Health* 2014, 68(1):6-12.

46. Nakamura T, Hashizume M, Ueda K, Kubo T, Shimizu A, Okamura T, Nishiwaki Y: The relationship between Asian dust events and out-of-hospital cardiac arrests in Japan. *J Epidemiol* 2015, 25(4):289-296.

47. Yorifuji T, Suzuki E, Kashima S: Outdoor air pollution and out-of-hospital cardiac arrest in Okayama, Japan. *J Occup Environ Med* 2014, 56(10):1019-1023.

48. Xia R, Zhou G, Zhu T, Li X, Wang G: Ambient Air Pollution and Out-of-Hospital Cardiac Arrest in Beijing, China. *International journal of environmental research and public health* 2017, 14(4):423.

49. Kang S-H, Heo J, Oh I-Y, Kim J, Lim W-H, Cho Y, Choi E-K, Yi S-M, Do Shin S, Kim H: Ambient air pollution and out-of-hospital cardiac arrest. *International journal of cardiology* 2016, 203:1086-1092.

50. Park SK, O'Neill MS, Vokonas PS, Sparrow D, Schwartz J: Effects of air pollution on heart rate variability: the VA normative aging study. *Environmental health perspectives* 2005, 113(3):304-309.

51. Dockery DW, Luttmann-Gibson H, Rich DQ, Link MS, Mittleman MA, Gold DR, Koutrakis P, Schwartz JD, Verrier RL: Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. *Environmental health perspectives* 2005, 113(6):670-674.

52. Rich DQ, Schwartz J, Mittleman MA, Link M, Luttmann-Gibson H, Catalano PJ, Speizer FE, Dockery DW: Association of short-term ambient air pollution concentrations and ventricular arrhythmias. *American Journal of Epidemiology* 2005, 161(12):1123-1132.

53. Chen CH, Chan CC, Chen BY, Cheng TJ, Leon Guo Y: Effects of particulate air pollution and ozone on lung function in non-asthmatic children. *Environ Res* 2015, 137:40-48.

54. Int Panis L, Provost EB, Cox B, Louwies T, Laeremans M, Standaert A, Dons E, Holmstock L, Nawrot T, De Boever P: Short-term air pollution exposure decreases lung function: a repeated measures study in healthy adults. *Environmental health : a global access science source* 2017, 16(1):60.

55. Yang Q, Chen Y, Krewski D, Burnett RT, Shi Y, McGrail KM: Effect of short-term exposure to low levels of gaseous pollutants on chronic obstructive pulmonary disease hospitalizations. *Environ Res* 2005, 99(1):99-105.

56. Zhang S, Li G, Tian L, Guo Q, Pan X: Short-term exposure to air pollution and morbidity of COPD and asthma in East Asian area: A systematic review and meta-analysis. *Environ Res* 2016, 148:15-23.

57. Ruidavets J-B, Cournot M, Cassadou S, Giroux M, Meybeck M, Ferrières J: Ozone Air Pollution Is Associated With Acute Myocardial Infarction. *Circulation* 2005, 111(5):563.

58. Choi M, Curriero FC, Johantgen M, Mills MEC, Sattler B, Lipscomb J: Association between ozone and emergency department visits: an ecological study. *Int J Environ Heal R* 2011, 21(3):201-221.

59. Qiu H, Tian L, Ho K-f, Pun VC, Wang X, Yu ITS: Air pollution and mortality: Effect modification by personal characteristics and specific cause of death in a case-only study. *Environmental Pollution* 2015, 199:192-197.

60. Bell ML, Zanobetti A, Dominici F: Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. *American journal of epidemiology* 2013:kwt090.

61. Medina-Ramón M, Schwartz J: Who is more vulnerable to die from ozone air pollution? *Epidemiology* 2008, 19(5):672-679.

62. Cakmak S, Dales RE, Angelica Rubio M, Blanco Vidal C: The risk of dying on days of higher air pollution among the socially disadvantaged elderly. *Environmental research* 2011, 111(3):388-393.

63. Goldberg MS, Burnett RT, Brook J, Bailar JC, Valois M-F, Vincent R: Associations between daily cause-specific mortality and concentrations of ground-level ozone in Montreal, Quebec. *American journal of epidemiology* 2001, 154(9):817-826.

64. Poland GA, Ovsyannikova IG, Kennedy RB, Lambert ND, Kirkland JL: A systems biology approach to the effect of aging, immunosenescence and vaccine response. *Current opinion in immunology* 2014, 29:62-68.

65. Bell ML, Dominici F, Samet JM: A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. *Epidemiology (Cambridge, Mass)* 2005, 16(4):436.

66. Goldberg MS, Burnett RT, Stieb DM, Brophy JM, Daskalopoulou SS, Valois M-F, Brook JR: Associations between ambient air pollution and daily mortality among elderly persons in Montreal, Quebec. *Science of The Total Environment* 2013, 463–464(0):931-942.

67. Forastiere F, Stafoggia M, Picciotto S, Bellander T, D'Ippoliti D, Lanki T, von Klot S, Nyberg F, Paatero P, Peters A: A case-crossover analysis of out-of-hospital coronary deaths and air pollution in Rome, Italy. *American journal of respiratory and critical care medicine* 2005, 172(12):1549-1555.

68. Bell ML, Zanobetti A, Dominici F: Who is more affected by ozone pollution? A systematic review and meta-analysis. *American journal of epidemiology* 2014, 180(1):15-28.

69. Nuvolone D, Balzi D, Pepe P, Chini M, Scala D, Giovannini F, Cipriani F, Barchielli A: Ozone short-term exposure and acute coronary events: a multicities study in Tuscany (Italy). *Environ Res* 2013, 126:17-23.

70. Medina-Ramon M, Schwartz J: Who is more vulnerable to die from ozone air pollution? *Epidemiology (Cambridge, Mass)* 2008, 19(5):672-679.

71. Anderson HR, Spix C, Medina S, Schouten JP, Castellsague J, Rossi G, Zmirou D, Touloumi G, Wojtyniak B, Ponka A *et al*: Air pollution and daily admissions for

chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. *Eur Respir J* 1997, 10(5):1064-1071.

72. Bell ML, Dominici F, Samet JM: A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. *Epidemiology (Cambridge, Mass)* 2005, 16(4):436-445.

73. Ensor KB, Raun LH, Persse D: A case-crossover analysis of out-of-hospital cardiac arrest and air pollution. *Circulation* 2013:CIRCULATIONAHA. 113.000027.

74. Pradeau C, Rondeau V, Lévèque E, Guernion P-Y, Tentillier E, Thicoipé M, Brochard P: Air pollution and activation of mobile medical team for out-of-hospital cardiac arrest. *The American journal of emergency medicine* 2015, 33(3):367-372.

75. Rosenthal FS, Kuisma M, Lanki T, Hussein T, Boyd J, Halonen JI, Pekkanen J: Association of ozone and particulate air pollution with out-of-hospital cardiac arrest in Helsinki, Finland: evidence for two different etiologies. *Journal of Exposure Science and Environmental Epidemiology* 2013, 23(3):281.

76. Yorifuji T, Suzuki E, Kashima S: Outdoor air pollution and out-of-hospital cardiac arrest in Okayama, Japan. *J Occup Environ Med* 2014, 56(10):1019-1023.

77. Arjomandi M, Wong H, Donde A, Frelinger J, Dalton S, Ching W, Power K, Balmes JR: Exposure to medium and high ambient levels of ozone causes adverse systemic inflammatory and cardiac autonomic effects. *American journal of physiology Heart and circulatory physiology* 2015, 308(12):H1499-1509.

78. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L: Effects of air pollution on the incidence of myocardial infarction. *Heart* 2009, 95(21):1746.

79. Ghanbari Ghozikali M, Heibati B, Naddafi K, Kloog I, Oliveri Conti G, Polosa R, Ferrante M: Evaluation of Chronic Obstructive Pulmonary Disease (COPD) attributed to atmospheric O3, NO2, and SO2 using Air Q Model (2011-2012 year). *Environ Res* 2016, 144(Pt A):99-105.

80. Ghozikali MG, Mosaferi M, Safari GH, Jaafari J: Effect of exposure to O(3) , NO(2), and SO(2) on chronic obstructive pulmonary disease hospitalizations in Tabriz, Iran. *Environ Sci Pollut Res Int* 2015, 22(4):2817-2823.

81. Li J, Sun S, Tang R, Qiu H, Huang Q, Mason TG, Tian L: Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2016, 11:3079-3091.

82. Levy D, Sheppard L, Checkoway H, Kaufman J, Lumley T, Koenig J, Siscovick D: A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. *Epidemiology (Cambridge, Mass)* 2001, 12(2):193-199.

83. Rosenthal FS, Carney JP, Olinger ML: Out-of-Hospital Cardiac Arrest and Airborne Fine Particulate Matter: A Case–Crossover Analysis of Emergency Medical Services Data in Indianapolis, Indiana. *Environmental health perspectives* 2008, 116(5):631.

84. Silverman RA, Ito K, Freese J, Kaufman BJ, De Claro D, Braun J, Prezant DJ: Association of ambient fine particles with out-of-hospital cardiac arrests in New York City. *American journal of epidemiology* 2010, 172(8):917-923.

85. Sullivan J, Ishikawa N, Sheppard L, Siscovick D, Checkoway H, Kaufman J: Exposure to ambient fine particulate matter and primary cardiac arrest among persons

with and without clinically recognized heart disease. *American Journal of Epidemiology* 2003, 157(6):501-509.

86. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, Feychting M, Ljung R: The Swedish cause of death register. *Eur J Epidemiol* 2017.

87. Environmental epidemiology: Study methods and application: Oxford university press; 2009.

88. Dahlquist M, Raza A, Bero-Bedada G, Hollenberg J, Lind T, Orsini N, Sjogren B, Svensson L, Ljungman PL: Short-term departures from an optimum ambient temperature are associated with increased risk of out-of-hospital cardiac arrest. *Int J Hyg Environ Health* 2016, 219(4-5):389-397.

89. Ito K, De Leon SF, Lippmann M: Associations between ozone and daily mortality - Analysis and meta-analysis. *Epidemiology* 2005, 16(4):446-457.

90. Zhang Y, Huang W, London SJ, Song G, Chen G, Jiang L, Zhao N, Chen B, Kan H: Ozone and daily mortality in Shanghai, China. *Environmental health perspectives* 2006, 114(8):1227-1232.

91. Samoli E, Peng R, Ramsay T, Pipikou M, Touloumi G, Dominici F, Burnett R, Cohen A, Krewski D, Samet J: Acute effects of ambient particulate matter on mortality in Europe and North America: results from the APHENA study. *Environmental health perspectives* 2008, 116(11):1480.

92. Saez M, Ballester F, Barcelo MA, Perez-Hoyos S, Bellido J, Tenias JM, Ocana R, Figueiras A, Arribas F, Aragones N *et al*: A combined analysis of the short-term effects of photochemical air pollutants on mortality within the EMECAM project. *Environmental health perspectives* 2002, 110(3):221-228.

93. Zanobetti A, Schwartz J: Mortality displacement in the association of ozone with mortality: an analysis of 48 cities in the United States. *Am J Respir Crit Care Med* 2008, 177(2):184-189.

94. Samoli E, Zanobetti A, Schwartz J, Atkinson R, LeTertre A, Schindler C, Perez L, Cadum E, Pekkanen J, Paldy A *et al*: The temporal pattern of mortality responses to ambient ozone in the APHEA project. *J Epidemiol Community Health* 2009, 63(12):960-966.

95. Le Tertre A, Quenel P, Eilstein D, Medina S, Prouvost H, Pascal L, Boumghar A, Saviuc P, Zeghnoun A, Filleul L *et al*: Short-term effects of air pollution on mortality in nine French cities: a quantitative summary. *Archives of environmental health* 2002, 57(4):311-319.

96. Pascal M, Wagner V, Chatignoux E, Falq G, Corso M, Blanchard M, Host S, Larrieu S, Pascal L, Declercq C: Ozone and short-term mortality in nine French cities: Influence of temperature and season. *Atmospheric Environment* 2012, 62:566-572.

97. Wong CM, Vichit-Vadakan N, Vajanapoom N, Ostro B, Thach TQ, Chau PY, Chan EK, Chung RY, Ou CQ, Yang L *et al*: Part 5. Public health and air pollution in Asia (PAPA): a combined analysis of four studies of air pollution and mortality. *Research report (Health Effects Institute)* 2010(154):377-418.

98. Anderson HR, Atkinson RW, Peacock J, Marston L, Konstantinou K: Meta-analysis of time-series studies and panel studies of particulate matter (PM) and ozone (O3): report of a WHO task group. 2004.

99. O'Neill MS, Veves A, Sarnat JA, Zanobetti A, Gold DR, Economides PA, Horton ES, Schwartz J: Air pollution and inflammation in type 2 diabetes: a mechanism for susceptibility. *Occup Environ Med* 2007, 64(6):373-379.

100. Mathers C: The global burden of disease: 2004 update: World Health Organization; 2008.

101. Medina-Ramon M, Zanobetti A, Schwartz J: The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol* 2006, 163(6):579-588.

102. Ko FW, Tam W, Wong TW, Chan DP, Tung AH, Lai CK, Hui DS: Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. *Thorax* 2007, 62(9):780-785.

103. Chugh SS, Kelly KL, Titus JL: Sudden cardiac death with apparently normal heart. *Circulation* 2000, 102(6):649-654.

104. Kannel WB, Schatzkin A: Sudden death: lessons from subsets in population studies. *J Am Coll Cardiol* 1985, 5(6 Suppl):141B-149B.

105. Raza A, Bellander T, Bero-Bedada G, Dahlquist M, Hollenberg J, Jonsson M, Lind T, Rosenqvist M, Svensson L, Ljungman PL: Short-term effects of air pollution on out-of-hospital cardiac arrest in Stockholm. *European heart journal* 2013, 35(13):861-868.

106. Straney L, Finn J, Dennekamp M, Bremner A, Tonkin A, Jacobs I: Evaluating the impact of air pollution on the incidence of out-of-hospital cardiac arrest in the Perth Metropolitan Region: 2000–2010. *J Epidemiol Community Health* 2013:jech-2013-202955.

107. Zhao R, Chen S, Wang W, Huang J, Wang K, Liu L, Wei S: The impact of short-term exposure to air pollutants on the onset of out-of-hospital cardiac arrest: A systematic review and meta-analysis. *International Journal of Cardiology* 2017, 226:110-117.

108. Deo R, Albert CM: Epidemiology and genetics of sudden cardiac death. *Circulation* 2012, 125(4):620-637.

109. Estes NAM: Predicting and Preventing Sudden Cardiac Death. *Circulation* 2011, 124(5):651-656.

110. Joundi RA, Rabinstein AA, Nikneshan D, Tu JV, Fang J, Holloway R, Saposnik G: Cardiac Arrest in Acute Ischemic Stroke: Incidence, Predisposing Factors, and Clinical Outcomes. *Journal of Stroke and Cerebrovascular Diseases* 2016, 25(7):1644-1652.

111. Chen C, Zhao B, Weschler CJ: Assessing the influence of indoor exposure to "outdoor ozone" on the relationship between ozone and short-term mortality in US communities. *Environmental health perspectives* 2012, 120(2):235.

112. Weschler CJ, Shields HC, Naik DV: Indoor ozone exposures. *Japca* 1989, 39(12):1562-1568.

113. Weschler CJ: Ozone in indoor environments: concentration and chemistry. *Indoor air* 2000, 10(4):269-288.

114. Langer S, Bekö G, Bloom E, Widheden A, Ekberg L: Indoor air quality in passive and conventional new houses in Sweden. *Building and Environment* 2015, 93(Part 1):92-100.

115. Laumbach R, Meng Q, Kipen H: What can individuals do to reduce personal health risks from air pollution? *Journal of thoracic disease* 2015, 7(1):96.

116. Chung KF, Adcock IM: Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction. *Eur Respir J* 2008, 31(6):1334-1356.

117. Uno K, Nicholls SJ: Biomarkers of inflammation and oxidative stress in atherosclerosis. *Biomark Med* 2010, 4(3):361-373.

118. Li F, Wiegman C, Seiffert JM, Zhu J, Clarke C, Chang Y, Bhavsar P, Adcock I, Zhang J, Zhou X *et al*: Effects of N-acetylcysteine in ozone-induced chronic obstructive pulmonary disease model. *PLoS One* 2013, 8(11):e80782.

119. Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS: The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *Am J Respir Crit Care Med* 2007, 176(4):370-376.

120. Devlin RB, Duncan KE, Jardim M, Schmitt MT, Rappold AG, Diaz-Sanchez D: Controlled exposure of healthy young volunteers to ozone causes cardiovascular effects. *Circulation* 2012, 126(1):104-111.

121. Kim CS, Alexis NE, Rappold AG, Kehrl H, Hazucha MJ, Lay JC, Schmitt MT, Case M, Devlin RB, Peden DB *et al*: Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours. *Am J Respir Crit Care Med* 2011, 183(9):1215-1221.

122. Thompson AM, Zanobetti A, Silverman F, Schwartz J, Coull B, Urch B, Speck M, Brook JR, Manno M, Gold DR: Baseline repeated measures from controlled human exposure studies: associations between ambient air pollution exposure and the systemic inflammatory biomarkers IL-6 and fibrinogen. *Environmental health perspectives* 2010, 118(1):120-124.

123. Jia X, Song X, Shima M, Tamura K, Deng F, Guo X: Acute effect of ambient ozone on heart rate variability in healthy elderly subjects. *J Expo Sci Environ Epidemiol* 2011, 21(5):541-547.

124. Shields KN, Cavallari JM, Hunt MJ, Lazo M, Molina M, Molina L, Holguin F: Traffic-related air pollution exposures and changes in heart rate variability in Mexico City: a panel study. *Environmental health : a global access science source* 2013, 12:7.

125. Zanobetti A, Gold DR, Stone PH, Suh HH, Schwartz J, Coull BA, Speizer FE: Reduction in heart rate variability with traffic and air pollution in patients with coronary artery disease. *Environmental health perspectives* 2010, 118(3):324-330.

126. Weichenthal S, Kulka R, Dubeau A, Martin C, Wang D, Dales R: Traffic-related air pollution and acute changes in heart rate variability and respiratory function in urban cyclists. *Environmental health perspectives* 2011, 119(10):1373-1378.

127. Zanobetti A, Canner MJ, Stone PH, Schwartz J, Sher D, Eagan-Bengston E, Gates KA, Hartley LH, Suh H, Gold DR: Ambient pollution and blood pressure in cardiac rehabilitation patients. *Circulation* 2004, 110(15):2184-2189.

128. Chuang KJ, Yan YH, Cheng TJ: Effect of air pollution on blood pressure, blood lipids, and blood sugar: a population-based approach. *J Occup Environ Med* 2010, 52(3):258-262.

129. Schoonhoven L: Essential epidemiology: An introduction for students and health professionals. *J Clin Nurs* 2006, 15(9):1210-1210.

130. Brown KW, Sarnat JA, Suh HH, Coull BA, Koutrakis P: Factors influencing relationships between personal and ambient concentrations of gaseous and particulate pollutants. *Science of The Total Environment* 2009, 407(12):3754-3765.

131. Ingelsson E, Arnlov J, Sundstrom J, Lind L: The validity of a diagnosis of heart failure in a hospital discharge register. *Eur J Heart Fail* 2005, 7(5):787-791.

132. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO: External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011, 11:450.

133. Hollenberg J, Bång A, Lindqvist J, Herlitz J, Nordlander R, Svensson L, Rosenqvist M: Difference in survival after out-of-hospital cardiac arrest between the two largest cities in Sweden: a matter of time? *Journal of internal medicine* 2005, 257(3):247-254.

134. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B: Time series regression studies in environmental epidemiology. *Int J Epidemiol* 2013, 42(4):1187-1195.

135. Curriero FC, Heiner KS, Samet JM, Zeger SL, Strug L, Patz JA: Temperature and mortality in 11 cities of the eastern United States. *Am J Epidemiol* 2002, 155(1):80-87.

136. Jhun I, Fann N, Zanobetti A, Hubbell B: Effect modification of ozone-related mortality risks by temperature in 97 US cities. *Environ Int* 2014, 73:128-134.

137. Maclure M: The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991, 133(2):144-153.

138. Fung KY, Krewski D, Chen Y, Burnett R, Cakmak S: Comparison of time series and case-crossover analyses of air pollution and hospital admission data. *International Journal of Epidemiology* 2003, 32(6):1064-1070.

139. Berglind N: Cardiovascular and respiratory effects of air pollution : application of different observational study designs and analysis approaches. Karolinska Institutet; 2017.

140. Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Atkinson R, Le Tertre A, Bobros J, Celko M, Goren A *et al*: The temporal pattern of mortality responses to air pollution: a multicity assessment of mortality displacement. *Epidemiology (Cambridge, Mass)* 2002, 13(1):87-93.

141. Fosu GB: Implications of Mortality and Morbidity for Health-Care-Delivery in Ghana. *Sociol Health Ill* 1986, 8(3):252-277.